PROBLEMS IN SECURING INFORMED CONSENT OF SUBJECTS IN EXPERIMENTAL TRIALS OF UNAPPROVED DRUGS AND DEVICES

Y 4.SM 1:103-85

Problems in Securing Informed Conse...

HEARING

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY

OF THE

COMMITTEE ON SMALL BUSINESS
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

WASHINGTON, DC, MAY 23, 1994

Printed for the use of the Committee on Small Business

Serial No. 103–85

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PROBLEMS IN SECURING INFORMED CONSENT OF SUBJECTS IN EXPERIMENTAL TRIALS OF UNAPPROVED DRUGS AND DEVICES

MONDAY, MAY 23, 1994

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON REGULATION, BUSINESS
OPPORTUNITIES, AND TECHNOLOGY,
COMMITTEE ON SMALL BUSINESS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:10 a.m., in room 2359–A, Rayburn House Office Building, Hon. Ron Wyden (chairman of the subcommittee) presiding.

Chairman WYDEN. The subcommittee will come to order.

Today the Subcommittee on Regulation, Business Opportunities and Technology examines the protection of our fellow citizens involved in clinical trials of unapproved drugs and medical devices.

We are especially concerned with the effectiveness of both public and private institutions, and individual researchers, charged with the supervision of persons who may become test subjects. The key ingredient in this process is the provision of informed consent; the demand that test candidates be fully informed of the risks and objectives of any unapproved drug or device test prior to giving their consent to be included in trials.

Most in medical science view this as a fundamental patient right. In this country, even in life or death situations, competent individuals have a basic right to refuse treatment. This right is especially important in decisions involving unapproved products.

In practice, however, the provision of informed consent is inconsistently applied. Turf protecting Federal agencies have produced contradictory and confusing policies, which put vulnerable Americans at risk, frustrate drug and device companies, and stymie medical research.

This issue is terribly complex. Our society demands that potentially life saving new drugs and devices are tested for safety and effectiveness, and are brought to market quickly with as little extra cost to manufacturers as possible.

This process requires test subjects. Some of the persons—individuals with head injuries, the mentally or emotionally disturbed, young children—may not be legally competent at the time of the trial. Informed consent in the classic sense may not be possible.

The Chair believes that fortunately there are practical methods for obtaining waivers in many of these cases. But the safe, sound

and ethical procedure required to do so demands a finely tuned, cooperative and collaborative relationship between first, the individual researcher, second, the hospital conducting the trials and third, the appropriate Federal agencies supervising both.

In the best of all possible worlds, these parts of the research oversight puzzle would fit together smoothly and consistently. After a year long investigation by the subcommittee including examination of confidential government files, it is apparent that too often breakdowns occur.

The subcommittee's particular interest is the degree of conflict on informed consent requirements between the Food and Drug Administration and other Federal agencies, most especially the Office for Protection from Research Risks. Because of this conflict, responsible companies and researchers often are paralyzed as a result of delay and confusion. A minority of companies, however, see the system's current loopholes as a high speed lane to circumvent sound practice and good procedure.

Dr. Jay Katz of Yale, an eminent legal scholar on this subject and one of today's witnesses, puts the issue squarely: "The radical transformation of medical practice which has led to an increasing number of patients being used as subjects of research for the sake of medical science—has not been accompanied by a thoroughgoing reappraisal of physicians' ethical obligations."

Another of our witnesses, Dr. Arthur Caplan of the University of Pennsylvania, has underscored the problem by calling the provision of informed consent in emergency room situations "a regulatory swamp."

Current Federal rules and guidelines encourage individual hospitals through their institutional review boards, to customize informed consent procedures. This situation has lead to the development of a creature known as deferred consent, the provision of the patient's permission after experimentation has begun.

The subcommittee intends to examine this concept carefully. The FDA tells us, in essence, that deferred consent doesn't exist; that it cannot take the place of informed consent procedures, or an FDA exception to consent. The fact is some hospitals are using it. This bizarre situation, where hospitals employ research standards regarded as illegitimate by the Federal Government, encourages the phenomenon of what one FDA official described to subcommittee staff as "institutional review board shopping." Quite simply, while the majority of companies and researchers act conservatively in order to protect trial subjects, some cut corners and "game" the system to find forums with a cavalier attitude toward informed consent.

What is the result? An attorney for one device manufacturer told subcommittee staff recently that since his client was testing an unapproved cardiac resuscitation device informed consent wasn't really required.

Their subjects, he said, had no pulse, weren't breathing, and for all practical purposes were already dead.

I intend to question the FDA witnesses today about this development as well as the development of so called free standing institutional review boards, IRB's, which operate independently of universities and hospitals, sometimes in a profit making capacity, but ap-

parently with the same standing as hospital IRB's. These hybrids may be insufficiently regulated.

Finally, there seems to be a troublesome conflict of interest between the scope and mission of hospital institutional review boards and the need for hospitals as institutions to earn a living. Clinical trials are a multibillion dollar per year business. The Federal Government alone, through the National Institutes of Health, funds something in the range of $5 billion per year in human research activity, at thousands of sites throughout the research community. For many healthcare facilities, these revenues are important. In weighing the ethical problems of a particular experiment with human subjects, cash strapped, decisionmakers may be hard pressed to deny researchers their trials, or trial dollars.

The challenge is to remedy a system that is under extraordinary stress. As we have stated, the majority of companies and researchers are responsible, and subjects in their trials are being properly protected. It is important to encourage innovation by granting local hospital institutional review boards a fair degree of autonomy, because that's where needed research innovation will take place.

A Federal Government, one size fits all, cookie cutter approach to medical research will create as many problems as it solves.

However, Federal regulators must provide a stronger safety net to protect all subjects. Informed consent, must be protected and nurtured as a fundamental principle.

Before we go ahead with our witnesses, let me recognize Mr. Combest of Texas. On these matters, as in all other areas, we work in a bipartisan way. I recognize the gentleman from Texas.

Mr. COMBEST. Thank you, Mr. Chairman. This morning the subcommittee will hear the troubling confusion of conflicting Federal regulations regarding experimental treatments for incapacitated humans in life or death situations. I plan to focus on how current informed consent guidelines are inadequate for patients, doctors and small companies involved in research efforts to develop life-saving technologies. I hope the outcome of this hearing will be swift action on the part of Secretary Shalala to harmonize the current foggy rules established by the Department of Health and Human Services (HHS) and its regulatory agency, the Food and Drug Administration (FDA).

Everyone agrees that all competent patients have the fundamental right to approve or disapprove a proposed experimental treatment. It is a clear cut principal that is certainly blurred for those patients unable to relay their wishes to health care professionals in a moment of crisis.

This morning some will suggest that research on head injury and cardiac patients should be completed only if patients can give their clear preapproval. I strongly disagree with this view. I believe it is implausible to believe that these accidents can be scheduled to accommodate researchers. Enrolling only likely victims would clearly skew trial results. In heart attack victims and head injury patients the window of opportunity for experimental treatment is so short and the frequent outcome is so menacing that informed consent is clearly not viable in all cases.

Imagine if rigid, waiverless informed consent rules were in place years ago, would life saving technologies like the defibrillator still

be in the prospective testing stage? If we are to develop the next generation of technologies for head injury and cardiac patients we must move research forward but only through legitimate trials where well thought out protocols are the rule, not the exception.

I believe that harmonizing the HHS and FDA regulations are necessary along with streamlining the current approval process for new drugs and devices. The status quo hurts all parties involved. Patients may not have access to promising breakthrough technologies. Researchers may be delayed in their discoveries because hospitals are fearful to move trials forward because of the confusion. Small companies are certainly hurt when media reports link them to so called improper actions because of murky regulations. No section of the American public can afford further delays in the development of life saving technologies.

Mr. Chairman, I would like to also ask unanimous consent that a statement that is being prepared by Congressman Machtley's staff be able to be added to part of the record. Mr. Machtley, as you know, is a member of the full committee and does represent a hospital that is in question today.

Chairman WYDEN. Without objection Mr. Machtley's statement will be entered in the record at this point and other colleagues will enter statements as well. The record will be held open for that.

[Mr. Machtley's statement may be found in the appendix.]

Chairman WYDEN. Our witnesses on panel one are Gregory Aller of Los Angeles; Mr. Frank Palin of Coventry, Rhode Island, Jeffrey D. Koepsell, president, CardioLogic Systems, Inc., Baltimore; Arthur Caplan, Ph.D., Center for Bioethics, University of Pennsylvania, Philadelphia; and Jay Katz, M.D., Yale Law School

Gentlemen, it is the practice of the Subcommittee on Regulation to swear all witnesses. Some, like Dr. Caplan, who have been here before know about our rules and procedures.

Do any of you have objection to being sworn as a witness today?

Please rise and raise your right hands.

[Witnesses sworn.]

Chairman WYDEN. We welcome all of you and very much appreciate your cooperation. As counsel to the staff has told you, we would like you to try to keep your prepared remarks to about 5 minutes or so. We will enter your full statement into the hearing record in its entirety and we appreciate everybody adhering to the 5-minute rule.

Mr. Aller, welcome.

GREGORY ALLER, JUNIOR, UCLA

Mr. ALLER. Thank you, Mr. Chairman and honorable members of the subcommittee.

My name is Greg Aller. I am a Junior at UCLA, majoring in political science. I come today to describe my experience in a schizophrenia research experiment at UCLA. In addition, 3 families from the UCLA Program asked me to speak on their behalf.

Back in 1987 I was diagnosed with schizophrenia. After being referred as a patient to the UCLA Aftercare Clinic for treatment, I had the experience of becoming not a patient but a subject in high risk research. Though I signed a consent form, it turned out to be deceptive because it omitted what the research was really all

about. The National Institutes of Health Office for Protection From Research Risks ruled on May 11, 1994 that the consent forms were not legally valid under Federal regulations because UCLA omitted foreseeable risks and alternative treatments. Over 100 persons participated in this research from 1979 to 1994, nearly 15 years.

The consent forms I signed did not indicate the real purpose of the research which was to study the relapse of patients. The researchers had published a scientific paper in the Journal of Abnormal Psychology, attached to my testimony, claiming that the study was an improvement over previous retrospective studies because this study was a prospective design that insured patients had severe or extremely severe relapses.

Independent psychiatrists, psychologists and bioethicists confirmed our finding. We never knew any of these facts until much later.

The UCLA researchers first put everyone on one medication and one standard dose, adhering to a strict scientific protocol. The type of antipsychotic medication used was Prolixin. The researchers did not follow the drug manufacturer's instructions that medication should be adjusted to the individual needs of the patient and they did not tell patients that they were in an experiment where the patient's welfare was secondary to the research goals.

In this first phase of the experiment I was lucky. Though some patients had a poor response to the standard dose, the standardized dose practically eliminated all of my delusions and made it possible for me to think relatively clearly. Since I have been diagnosed with paranoid schizophrenia, relief from the symptoms greatly improved my life. My family and I were ecstatic. I enrolled at Santa Monica College and during the next year, I earned a 3.8 GPA, got on the Dean's List and worked 15 hours a week. I was proud of what I was accomplishing. It was certainly the best year of my adult life. But what would follow became the very worst year of my life.

The doctors asked me to go off medication to prevent the onset of a potentially irreversible movement disorder called tardive dyskinesia. In mid-1989, Dr. Neuchterlein, the principal investigator met with my parents and I, and in response to my mother's concern about potential relapse, he promised my parents that if I had a return of symptoms the medication would be reinstated. Dr. Neuchterlein said that since my parents knew me best, when they best reported symptoms, I would get my medication back.

My mother asked Dr. Neuchterlein about this matter several times, stating that our family did not want to see a return of symptoms, especially since I was doing so well and was close to realizing my dream of transferring to UCLA. We trusted the doctors, and I agreed to go off the medication. What we didn't know was that the researchers had another agenda.

As my parents would later discover in the protocols, grant applications and summary reports, the researchers had claimed that they were studying exacerbation and relapse that results from standardized doses of medication and withdrawal of medication. This is not what they told patients and their families.

During the second phase of the experiment, my symptoms gradually returned, but this was the research plan for all patients with-

drawing from medication. However, this time my symptoms were much more severe than the symptoms of the onset of my schizophrenia. What ensued was a nightmare. My ability to concentrate fell apart.

I was unable to do school work. I became manic and hyperactive. Some days I would hardly sleep at all. One night I woke up screaming actually believing that I was sprouting another leg. I started to have paranoid delusions about Government agents chasing me. I became violent with my father and threatened to kill him. I believed there were hidden cameras on the wall of my parents' living room. Much later, still in the delusional state, I started hitchhiking to Washington to assassinate President Bush. Though I had slipped back into paranoid symptoms, my doctor asked me if I felt I needed medication.

Since I was paranoid by that time, I said I was fine, I didn't need medication. Dr. Gitlin never really delved into what was really going on in my life. At one point during my psychotic relapse, I thought that the devil had taken possession of my mother by entering her body. I thought this was horrible for her, but I believe I could scare or cut the devil out of her. I grabbed the butcher knife in the kitchen and called to my mother. Before I could reach her, she fled into the bedroom and barricaded the door. My father was able to talk to me so that I put down the knife. I was willing because I thought that I had scared the devil out of her. Looking back, it is horrifying to consider what might have happened if my father had not been present.

Throughout my deterioration and disintegration from late 1989 to May, 1990, my father called the project's staff, telling them that he thought I needed medication. Both my mother and father met with Dr. Neuchterlein in January 1990, and he said that my symptoms might be fluctuating and temporary and the staff would watch me carefully. Dr. Neuchterlein persuaded my parents to wait. My father persisted in his angry phone calls, but the researchers said they did not agree with my parents' assessment. I suffered from months of psychotic experiences.

Finally, on May 15, 1990, my parents persuaded me to go back on medication. The same day, my father took me to UCLA and I received an injection of Prolixin, but over the next 6 months I didn't return to my former level of functioning.

My parents felt it was necessary to see the Vice Chancellor of Research, Albert Barber, to explain what happened and to ensure that these kinds of events didn't happen to other patients and families. On February 20, 1991, my parents met with Vice Chancellor Barber and other administrators. They told the UCLA staff that they believed a murder or suicide could likely occur under the conditions we had experienced.

I believed that my parents' warning was not taken seriously. At approximately the same time, in late February or early March 1991, the researchers withdrew medication from another patient, Antonio Lamadrid, a former UCLA student. After 5 years of treatment, the researchers expelled him from the program. When Tony was withdrawn from medication, he repeatedly told his UCLA case worker that he planned to commit suicide but the UCLA research-

ers never even bothered to inform the Lamadrid family of Tony's suicide threats.

Barely 5 weeks after my parents had warned the Vice Chancellor, on March 28, 1991, Tony walked up to the roof of UCLA; nine-story Boelter Hall and jumped to his death, fulfilling his plan to commit suicide. The police report on Tony's suicide stated that the Aftercare Clinic refused to permit the police investigator to talk to a witness and former patient from the Aftercare Clinic who had been staying with Tony prior to his suicide.

Later I learned from the Lamadrid family that a phone call to Tony's aunt or to any of Tony's three brothers, two of whom lived within minutes of Tony would have alerted the family instantly and they would have been there to help Tony, but the family never understood precisely what was happening until it was too late. Even after Tony's suicide, Tony's psychiatrist for the last 5 years, Michael Gitlin, never spoke to the Lamadrid family to offer a simple personal condolence.

OPRR investigated the suicide and communicated with the UCLA doctors, administrators and lawyers, but during the 3-year investigation OPRR never interviewed the Lamadrid family. OPRR reached its conclusions after reviewing evidence presented only by UCLA.

Let me describe what happened to the other subjects in this program. Gabrielle Guardino, nicknamed Gabby, suffered an excruciating reaction to the standard dose of Prolixin, yet her doctors would not break the protocol and switch her to another medication. Gabby's mother told me that the medication caused Gabby to vomit frequently, bite her tongue and the insides of her mouth until she bled, and Prolixin caused her to have the sensation of her skin crawling.

Although aware of Gabby's suffering, the doctors never told Gabby's mother about the alternative medications. What they did tell here was that Gabby would have to stay on the medication or she would have to leave the program. Finally, after 8 months, Gabby couldn't stand the effects of the medication anymore and she quit the program. A lot of terrible things happened to her. She was raped by two men when she was psychotic. She served time in jail.

Finally, an organization called Children of the Night found Gabby living in a park. Gabby's mother wrote a strong letter of complaint to UCLA back in 1985 carefully sending copies of her letter to UCLA's key psychiatric administrators, including Albert Barber, Vice Chancellor of Research. UCLA never wrote back to Sydelle Guardino.

As a patient, I find such research outside the boundaries of human decency. I ask you who would ever want to be kept in the dark about medications that might have helped?

Let me describe one more UCLA case. Frank De Balogh, Ph.D. asked me to speak on behalf of his younger sister Elizabeth. Elizabeth was living successfully at home. Then, as Frank De Balogh explained to me, the UCLA researchers decided to withdraw medication from Elizabeth. She suffered an extremely severe relapse. No informed consent had been obtained and the foreseeable risks from severe relapse had not been described to the family.

I quote from the report submitted to OPRR by Frank De Balogh. "One Saturday morning in May, 1985, I received an urgent call from my mother, who requested my help, saying that she could not handle Elizabeth. I found Elizabeth not speaking, not eating, not sleeping, pacing about pushing her mother away, turning lights on and off, opening and shutting doors and windows. In short, she was acting psychotic.

"When I called the UCLA phone number for help, all we got was a message that they would be available during business hours Monday through Friday and they could not be reached on the weekend. Dr. De Balogh states that UCLA had not provided emergency instructions or plans in the event of a relapse. Since immediate Medicare was necessary, Dr. De Balogh checked Elizabeth into the Los Angeles County U.S.C. Hospital, and Elizabeth has remained institutionalized since that episode in 1985."

Dr. De Balogh describes Elizabeth's current condition: Due to a fear of cars and freeways, Elizabeth is unwilling to visit any of her family members' homes. She is afraid to see her cousin, whom she considers to be a witch. She has continuous suspicions about her food being poisoned. She doesn't watch television in her room because she claims that she watches television in her mind. In short, she remains gravely disabled, most probably institutionalized and under conservatorship.

In addition to the failure to obtain valid informed consent, Dr. De Balogh highlights the lack of administrative oversight by the UCLA Neuropsychiatric Institute and the lack of medical emergency planning required for such high risk research.

Would I have ever signed the UCLA consent if I had been provided the full addition closure and I had known the real purpose of the study? Absolutely not. I don't think anyone else would have either. I don't believe that this research could have taken place with proper disclosure and informed consent. I believe that the researchers view people with schizophrenia as subhuman. I doubt whether any doctor who works at the UCLA Medical Center would ever allow a son or daughter to become a subject in this experiment. In fact, after I obtained a few of my patient records, OPRR confirmed that my psychiatrist's initials appeared next to white-outs, obliterations and alterations in my records.

Unfortunately, the end is not in sight. UCLA has experimented on hundreds of veterans with schizophrenia, without indicating foreseeable risks and alternative treatments in the informed consent forms. The Office for Protection From Research Risk has been sitting on that investigation for 15 months and for some reason has not issued a report about what happened to the veterans.

I would like to point out that I have never had an another relapse. I simply take my medication everyday. If anyone told me to stop taking medication, I wouldn't follow that advice. It was a terrifying and damaging experience.

People with schizophrenia suffer enough. The stigma of the illness frightens people. It is a very lonely life, I know. But those of us with schizophrenia really want the same things out of life that others want.

We do need treatment that helps us to become the best that we can be. To deliberately harm us without informed consent is uncon-

scionable. I told my father one evening when we went for a walk that I think I have half a life, but I do want to lead that half a life as fully as I can.

Sadly, even with the protocols showing that patients would be harmed by participation in the UCLA research, OPRR did not act promptly as it should have. Over a period of 3 years OPRR never interviewed a single patient in the UCLA Program. This upsets me. The Office for Protection From Research Risks is saying to 107 subjects with schizophrenia are worthless; Tony, Elizabeth, Gabby, and the others who were harmed in this program. It is the researchers that really matter.

Mr. Chairman and members of the subcommittee, I have one message today. The system does not protect human subjects; it protects the researchers. New legislation is needed.

I would like to add I have seen one of the witnesses, Dr. Don Rockwell of UCLA, director of the Neuro-psychiatric Institute. I had a chance to take a look at his statement this morning. I would like to point out a few things.

In UCLA's 1982 grant application, one of the specific aims was that the researchers wanted to see how long it would require to hospitalize a patient after withdrawal of medication. That is hardly standard community treatment. Further, the subcommittee should know that Dr. Rockwell is currently blocking access to State investigators to patient records so that the State is unable to review possible other violations of law.

Further, the subcommittee should know that the State of California found that Dr. Rockwell and UCLA had violated the laws of California by withholding my patient records for 2.5 years.

Further, all 53 patients withdrawn from medication had to go back on medication, a 100 percent adverse reaction. The consent form said that you may get better, you may stay the same or you may get worse. The consent forms should have said there is a 100 percent chance you will get worse. UCLA had material data and they omitted it from the consent form.

Finally, Dr. Rockwell claimed that UCLA got oral informed consent but as a patient and having known other patients, the UCLA contention is not true.

In closing, I wouldn't be here without deeply supportive family and their friends and the many experts who stood with us. Perhaps the researchers thought that the public would never find out what they were doing, but they were wrong. However, in spite of the evidence just like the doctors at Tuskegee and the doctors who conducted radiation experiments, the UCLA doctors claim that they did nothing wrong. I am grateful to you, Mr. Chairman, and members of the subcommittee for the rare opportunity to speak today.

Thank you.

[Mr. Aller's statement may be found in the appendix.]

Chairman WYDEN. Mr. Aller, thank you for your excellent statement. I will have some questions for you in a moment. I really appreciate the courage you showed in coming here; it is a pretty gutsy thing to come testify before Congress. I know this is the first time you have spoken out on this and we are going to follow up on the additional matters that you raised at the end of your statement.

They are extremely serious and we will be following up on those promptly.

Mr. Palin.

TESTIMONY OF FRANK PALIN, EMERGENCY ROOM TECHNICIAN, RHODE ISLAND HOSPITAL

Mr. PALIN. Mr. Chairman, members of the subcommittee, I am Frank Palin. I am an emergency room technician at Rhode Island Hospital. Research on human subjects plays an integral part in conquering new frontiers in health care. Continuing abuses of ethical guidelines by callous researchers threaten the continuance of future human investigations.

Human subject experimentation without informed consent continues to take place every day. The public needs the protection of strong, unambiguous laws to prevent the continuation of abusive research. I have been invited to appear before this subcommittee to provide an illustration of an abuse of human subject research that ignored informed consent. This study was chosen because of my intimate involvement in halting the process. I will attempt to convey a first-hand narrative of my activities as a patient advocate to protect this impaired population.

The alcohol/hypoglycemic study, which is Exhibit A within my written testimony, focused on intoxicated patients. According to written protocol, "patients cannot refuse to be part of this study, as they are technically not capable of refusing lifesaving care while intoxicated," which is in the study time line, Exhibit C. Blood was taken from intoxicated patients on arrival and at 4 hours and 8 hours. Staff was ordered not to feed the study patients until 8 hours after arrival.

The hospital's critical path for caring of substance abusing patients which is Exhibit B was revised in June 1993, fully 5 months before the study started. This revision required the use of a Breathalyzer instead of blood work to determine blood alcohol level. A major reason for the change was to decrease the violent reactions of patients who refuse to have their blood drawn.

Noncompliant patients who do not follow the rules are placed in four-point restraints. I brought a restraint with me. They will take the leather restraint, such as I have in my hand, it is wrapped around one arm, another arm, around both legs and then the patient is put sprawled on top of a stretcher on his stomach and he is tied there for many times hours at a time. Documentation usually states that the patient was restrained to protect self or others from injury. The reality of the situation usually is that the patient refused to have their blood drawn. They refused to comply with that. Forcing patients to participate in the study reintroduced the volatile situation.

I was instructed to do the 4-hour study blood draw from a restrained patient on the evening of November 7, 1993. I refused to follow the order. I cited a lack of informed consent and I also told management that participation in this study by drawing blood is against my moral, ethical and religious principles, and I also feel the study is illegal. I was immediately suspended and I fully expected to be fired Monday morning.

When we are talking about this patient population, we are not just talking about the so-called street bum or the homeless individual. These could be college students from Brown University or Providence College, could be my kids or your kids, or could be our brothers and sisters. Many times people are walking in, they have been drinking and they are looking for detox. We have a limited amount of facilities in Rhode Island for detox and they end up having to stay there until sober.

For all intents and purposes, they are incarcerated until they are sober. The doctors took advantage of this population to do research for the sake of research.

I felt very strongly that the study was illegal because body fluids were taken from patients who were not offered the opportunity to give informed consent. The individual rights—and that is a key point, the individual rights of human beings were being obliterated by the researchers.

I managed to stop the study, but I had to go through a lot. I started with my immediate supervisor. She referred me to Dr. Sucov, who wrote the study. I spoke to him and he felt he was right and he was going to continue the study.

The day the study started I left messages with Dr. Sucov, Dr. Jagminis and Dr. Woolard asking that they postpone it until I had a conversation with them and I wanted to bring a couple of advocates within the community who worked with chemically dependent people. They never responded to my call. Linda St. Angelo, the director of emergency room nursing called me later that day and told me that basically I would be found guilty of insubordination if I failed to follow hospital standards and refused to draw the blood. I looked it up in the hospital manual, insubordination, said you get fired if you say no to doing this.

At that point I said enough is enough. I hand-delivered a letter to the president of the hospital, William Kreykes, also the president of Brown University, Vartan Gregorian, the Dean of the Brown University Medical School, Donald Marsh and to Steven Brown from the ACLU asking that the study be stopped because I felt it was illegal, and there are a number of exhibits within my written testimony you will see those letters and the reasons I used.

The hospital started the study and it got rolling. At that point I said let's bring it up a notch. On 5 November I composed a letter which I sent to the Rhode Island attorney general, the Rhode Island Office of the U.S. Attorney and to many different offices within the Department of Health.

I also contacted just about every single member of the press I could think of, whether it be written press, radio, TV and any advocacy groups that deal with this constituency. Pressure by newspaper coverage, the American Civil Liberties Union and Government agencies forced the hospital to suspend the study and to reinstate me 12 days after I have been suspended from work on November 7 for refusing to participate in the study.

Patients were not told before participation or after discharge that they had been a research subject. According to Kenneth Arnold, Chief Legal Counsel of Rhode Island Hospital and Donald Marstein of Brown University Medical School, and a letter from Dr. Marsh, Exhibit H shows this, the Institutional Review Board gave re-

searchers permission to waive informed consent. Ignoring informed consent regulations seemed to be the rule rather than the exception here.

I will briefly describe multiple examples of Rhode Island Hospital's arrogance on this subject. The Institutional Review Board seems to be a rubber stamp for the hospital researchers. There are 16 members on Rhode Island Hospital's Institutional Review Board. Fourteen are hospital employees. One member is an attorney who is affiliated with the hospital's law firm and the last member is a pediatric psychiatrist with admitting privileges to the hospital. A similar alcoholic/hypoglycemia study was performed on approximately 300 patients in 1992.

This study included one blood draw. At no time was the patient told that their blood was being used for research. Two studies in 1992 and 1993 used something called the ALCO screen dipstick. The 1992 study included adults only, while the 1993 study included children and adults. Patients who were admitted to the emergency department with injuries sustained in an accident of any kind were studied for about 6 months in each study. Thousands were included in both studies.

Dipsticks were placed in the patient's mouth to measure alcohol use. Results were entered prominently on the cover sheet of the patient chart and permanent record. This is also a violation of patient confidentiality laws 42 CFR, part 2. Informed consent was not discussed with any study patients before, during or after their participation.

Informed consent was even omitted when a parent was present with their child. They were unaware of participation in a study and the chart entry about the study results.

One of the most appalling cases of research for the sake of research is an asthma study conducted with children by Dr. Robert Wright of Rhode Island Hospital described in exhibit L. This study is designed to measure descriptive assessment language used by doctors of children suffering from an asthma attack. The method used is for one physician to examine the child and document assessment findings. Then a second doctor repeats the examination and documents the assessment. The descriptive verbiage was going to be compared later. During the two examinations which can probably take up to a half-hour or more, the standard nebulizer treatment is withheld from the suffering child who is having difficulty breathing.

A child is sucking for air and having difficulty breathing and everybody has to ignore the child and can't treat the child. A child suffering from an asthma attack can quickly deteriorate, go into respiratory arrest and die.

Was this explained to the parent?

Would any parent consent if told the true dangers of participation? I don't think so. I aggressively attacked this study because of the inherent danger of a death of a child.

You are talking about someone who is graduating from nursing school and wants to be a pediatric nurse. I was appalled. Hospital officials when I met with them maintained that the study met informed consent regulations and refused to stop it. They offered to show me the study protocol and when I showed up the next morn-

ing to see it, it wasn't present. It was never offered to me. I could never see it.

The attitude of Dr. Wright and of Rhode Island Hospital can be best described with a quote from this asthma study letter, Exhibit L, which was posted on a public bulletin board within this inner city hospital. "I have a small daughter who depends on me to put food on the table. If I don't finish this study, my wife will probably leave me and I will end up penniless, drunk and smelly in south Providence." Is that a wonderful thing for a doctor to post on a public bulletin board in this inner city neighborhood of South Providence for everybody to read? I don't know what they are thinking about.

The Timi 9 Research Study is being conducted in 150 hospitals in the country. This Ciba-Geigy sponsored study of blood-thinning medication enrolls individuals who are in the midst of a heart attack. The form used for agreement to participate is proper.

However, the reality of the informed consent process is quite different. I have been in a trauma room and witnessed patients suffering from an excruciatingly painful heart attack. It is like having an elephant stand on your chest and the doctor goes up to the patient and says will you agree to let us use the study protocol? No other explanation or information is used. The patient in this kind of pain at that point would probably consent to being shot and killed if it took the pain away.

The consequences of my whistleblowing have been an unsuccessful attempt by the hospital to fire me back in November. I have also developed a problem with cardiac tachycardia that has forced me to take a temporary medical leave of absence. Since the hospital knew that I was testifying this week, they promptly timed another threat, which was delivered to me by certified mail last week which was a threat of termination.

I didn't look for a fight. I tried to go through channels. I tried to do things the right way. I was just acting as a patient advocate in my role as a future professional nurse. Hopefully, nursing leaders will stand behind me in my search for a career position in nursing.

All Federal agencies should make a thorough review of current statutes and regulations involving human subject experimentation. A joint committee of agency members should write new uniform regulations that apply to all human subject researchers.

These regulations must remove ambiguous language so an institutional review board can properly carry out their mission. Additionally, I believe that an ethics subject experimentation committee should be formed to audit the actions of institutional review boards including, as Mr. Aller suggested, interviewing the research subjects and to respond to complaints. Penalties for violations should include the loss of Federal funding for the researcher and the institution.

This threat would force the institutional review board to be more vigilant and to police the researching activities that are taking place within their facilities.

In closing, I wish to thank the subcommittee for the opportunity to discuss my concerns. I am willing to provide any other service

to my country and serve on any review committee that provides human rights protection for all. Thank you very much.

[Mr. Palin's statement may be found in the appendix.]

Chairman WYDEN. Mr. Palin, thank you very much for a very helpful and frightening bit of testimony. I am particularly struck by the fact that what you have described to us is something that you personally witnessed. It is not some sort of gossip or rumor mongering, but something that you actually saw, so it is really helpful to have you come and speak out in the way you have.

This subcommittee is especially interested in what happens to whistle-blowers and people who are willing to come forward. So, we are going to follow your situation very carefully, and I will have some questions for you in a few moments.

Mr. PALIN. Thank you.

Chairman WYDEN. Our next witness is Mr. Jeffrey D. Koepsell, president of CardioLogic Systems, Baltimore, Maryland. Welcome.

TESTIMONY OF JEFFREY D. KOEPSELL, PRESIDENT, CARDIOLOGIC SYSTEMS, INC., BALTIMORE

Mr. KOEPSELL. Thank you, Chairman Wyden.

I am Jeff Koepsell, president and CEO of CardioLogic Systems, Inc., a Baltimore-based venture capital backed small business.

The subcommittee has just heard and will be hearing additional testimony about some serious concerns regarding potential abuses regarding clinical trials and informed consent issues. I am here to discuss informed consent, but from an emergency medical research and small business perspective.

Current HHS and FDA regulations and/or the inflexible interpretation of these regulations concerning informed consent are threatening the advancement of medical technology and improved patient care in emergency medicine. If the winds of the existing regulatory climate do not change, then small businesses such as CardioLogic will be forced to close, larger businesses will move their operations to other countries, university hospitals will cease trauma and resuscitation research, and the American public stands to suffer the loss in lives and in jobs.

To be more graphic, if the current FDA informed consent regulations had been in effect in the 1950's, the defibrillators that save in excess of 50,000 lives each year could not have been tested on humans and would not be approved today.

Let me explain the dilemma in detail. Each year more than 300,000 people die from cardiac arrest. Since 1960, manual CPR has been used as a means of providing oxygenated blood to the heart and the brain. The rescuer presses on the sternum with a regular rhythm. The differences in the skill and strength of a rescuer as well as the inability of manual CPR to generate much blood flow, causes variability in success rate.

Studies show that the best manual CPR when coupled with defibrillation both in and out of hospital has a long-term survival rate of 15 percent. This means that 8 out of every 10 cardiac arrest patients are going to die and they do die.

In 1981, because of those dismal success rates for CPR, researchers at the Johns Hopkins University started looking at various alternatives to increase blood pressure and flow during cardiac ar-

rest. Over a 12-year period, they developed and tested a prototype vest-CPR system. The vest system is analogous to a large blood pressure cuff that wraps around the chest and is attached to a computerized pneumatic system that inflates and deflates 60 times per minute at pressures up to 250 millimeters of mercury.

During this 12-year period, vest-CPR went through multiple prototype stages: Three animal studies and two human clinical trials. The animal studies showed that vest-CPR was better than manual CPR because it increased arterial blood pressures, increased blood flow to the brain and to the heart, showed no increase in trauma, and increased survival to a prearrest neurological status.

Human clinical trials were then approved by the Johns Hopkins University Institutional Review Board and the FDA. Informed consent was waived for the following reasons: The positive results of the previous trials, patients would receive standard care prior to entering the study, there was no way of forecasting who would have a cardiac arrest, and obtaining consent in the face of a life-threatening emergency was not feasible.

The human study showed increased coronary profusion pressure, increased peak aortic pressure, increased return of spontaneous heart rate, increased 6-hour survival without any increase in trauma to the patients.

Researchers at Johns Hopkins believe that the vest-CPR system, if applied earlier in cardiac arrest and widely used, could double the long-term survival rate, that is neurologically intact long-term survival rate, saving an additional 45,000 lives a year in the United States alone.

CardioLogic Systems licensed the vest-CPR technology from Johns Hopkins in December of 1992. We then raised $5.9 million of venture capital for the vest-CPR system. Over the last 1½ years, we have spent $2.5 million on improving the safety and reliability of the vest-CPR system and developing a clinical protocol which is very similar to the Johns Hopkins study, and completing a 3,700 page IDE investigational device exemption for submission to the FDA.

I brought a copy of this IDE submission, which is located over here on the corner of the table, and I would like you to compare it to the 1988 IDE submission that was prepared by the Johns Hopkins University. This was 62 pages. Ours is 3,700 pages. It is obvious that the Federal Paperwork Reduction Act has really not addressed this area.

The comparison of these submissions points out the changes that are occurring in the regulatory medical device clinical trial arena. For the most part, we view these changes as positive because they foster a safer and more reliable medical industry. However, the line must be drawn at being asked to do the impossible or the unreasonable. In Johns Hopkins study waiver of informed consent was granted, but not in our study.

To obtain perspective informed consent, we will have to approach up to 260,000 patients to enroll 400 in our study at a cost that could be above $1.4 million. Principal investigators have already told us that prospective informed consent for the vest-CPR study would probably not be accepted by the IRB's. One principal investigator has already written to us to withdraw from the study. De-

spite our offer to pay for the staff to obtain informed consent, he felt it was too much of a burden on their patients and staff. The investigator wrote, "Even though CardioLogic would be willing to provide assistance in obtaining informed consent from these patients, it was felt that they would have significant anxiety and subsequent questions for their continuing care physicians."

His nurse managers concern about the informed consent requirement was the increased anxiety for the entire patient population, when only 1.5 percent of the patients would actually participate in this study. We would scare to death 300 patients a month that would never arrest."

I have included with my statement a 1988 analysis by Dr. Bruce Miller, reprinted from Critical Care Medicine. I believe this article sets forth for Congress and the agencies conditions which ethically justify research trials and resuscitative medicine without informed consent. The conditions give meaning to the term "minimal risk" in a way that appropriately balances the potential benefits and risks of resuscitation research.

They are that the patient is comatose; lifesaving treatment must be given immediately; given all available evidence, there is reason to believe that the probability of death or severe deficit with experimental or controlled therapy is not greater than the probability of death or severe deficit with the usual therapy; given all available evidence, there is reason to believe that the probability of normal or near normal outcome is greater on experimental or controlled therapy than on usual therapy; and that the study can provide evidence on whether there is a significant difference between experimental and controlled therapies and the incidents of normal or near normal survival.

The vest-CPR system is an ideal candidate to be considered for such an exception to informed consent based upon the above criteria.

I must emphasize that our company understands that the autonomy, safety, and well-being of patients must come first. We believe in our technology and that it can save and improve lives. We will follow the rules and have followed the rules. If we can convince hospital IRB's to participate in the vest-CPR study with informed consent, and we can enroll enough patients in a reasonable time period, that is, before we run out of money, and the results of our trial are statistically significant, then we could be able to apply to FDA for premarket approval, PMA, by the end of 1995.

By then, we will have exhausted our finances and will require an additional $3 million to get it through the 18- to 24-month FDA PMA process. By 1998, we should be able to start marketing. But the major market for vest-CPR is the first responder area—fire, rescue units, and ambulances—where 70 percent of cardiac arrests occur.

Our plan is to develop a portable vest-CPR system for that market. Without this market, CardioLogic will not survive.

Now comes the impossible. We have been told by the FDA that another clinical study will be required for the first responder market, including the need to obtain prospective informed consent. How this can be accomplished is unknown. The only response has

been, that is the regulation, it is up to you to figure out how to do it.

Flexibility in this regulatory area is vital. Clinicians, ethicists, and patient advocates should be allowed to share the decisions on emergency medical informed consent.

Chairman Wyden, Congressman Combest, you and your subcommittee have identified a complex area of Government policy which needs bold leadership and direction. There are and will continue to be appropriate circumstances for waiver of prospective informed consent for emergency resuscitative research. I ask you and your colleagues to work with the agencies to clarify the regulations and to allow appropriate emergency research to continue. Thank you.

Chairman WYDEN. Thank you very much, Mr. Koepsell, for an excellent statement.

[Mr. Koepsell's statement may be found in the appendix.]

Chairman WYDEN. I think you have really laid out very well for the subcommittee what this challenge is all about. You have said very bluntly that the rights of patients have got to come first. We appreciate that. At the same time, however, it has got to be possible for a small company like yourself to get a product to market without really having 1,000 cuts inflicted on you by Federal agencies to the point where you can't do business. Striking that balance is really right at the heart of what we are trying to do here.

So, we are going to have some questions for the FDA about new ways in which they can ensure that patient rights are protected while at the same time not putting folks like yourself through bureaucratic water torture, and we will be asking them some questions about it in a bit and have some questions for you as well.

Let me welcome Dr. Caplan, who has done exceptionally good work for many years in this complicated ethical field and has been before this subcommittee many times.

Dr. Caplan, we welcome you. Please proceed as you choose.

TESTIMONY OF ARTHUR CAPLAN, PH.D., CENTER FOR BIOETHICS, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA

Mr. CAPLAN. Thank you, Mr. Wyden. It is a pleasure to be in front of this subcommittee on this timely and important topic. I am pleased to see that the subcommittee is focusing attention here. It is appropriate, as we have heard from previous witnesses, and overdue.

I wanted to begin by just recounting three areas where I have seen problems arise with respect to the adequacy of informed consent in existing regulations to govern research.

The first doesn't involve someone who is comatose or in the middle of a catastrophic medical event. It was a situation at my school at the University of Minnesota, where I have been for the past 7 years. A young couple was told that their daughter was in the throes of respiratory failure and that they had 2 hours to decide whether one of them wanted to donate a lobe of lung to try and save their daughter. It is clearly an innovative and experimental procedure, although it wasn't in front of the IRB, because this was viewed as an emergency, an emergent problem.

The parents were competent. There was nothing wrong with them. But the circumstances under which the question comes makes one wonder about the adequacy of informed consent alone to protect the interests of a person asked to give up a piece of their own body to save their own child. Very few people are going to be able to say no to that request. Even if we presume that informed consent ought to be obtained, and I do, I am not sure how much we can credit it. Circumstances can be so coercive and overwhelming sometimes that informed consent falls away, I think, as an adequate protection.

Second, I was involved at Minnesota in looking at a device not unlike that Mr. Koepsell told us about, a different form of resuscitation device for individuals with cardiac arrest and respiratory failure out in the street. This is a device that was reported on not too long ago in the Journal of the American Medical Association, the Ambu pump.

One of the things that struck me about looking at that device and thinking about the ethical issues of where to try it, who should receive it and what should they be told, is that people presume oftentimes that if you are in the middle of a heart attack, a respiratory arrest, you would ask for anything to be tried to save your life.

The difficulty was that this particular device, and this may occur for other technologies and other types of drugs or innovations, held out the prospect of restoring heart function but maybe not neurological function, so that you might wind up having your heart working again but with severe brain damage if the device was not administered to you in a timely manner after your heart attack.

It is something that made us stop and realize it isn't the case that even in an emergency, doing something, even a desperate intervention, is always the best thing or something that everybody would choose to take on as a risk. So, I would like the subcommittee to realize that the choices here don't involve trying to figure out always how can we make it possible for something to happen; there are oftentimes tradeoffs and risks that have to be weighed.

The last example I want to mention to you is some research that took place involving people who had overdosed on PCP and an idea about a drug intervention that could be tried. We had young teenagers coming into the emergency room and the question was, could we try this new drug on them to see if it would alleviate their symptoms?

Again, a sudden overdose in an emergency context, questions coming up; what about the competency of young people and children and minors to be involved in this sort of research?

That actually let's me go to the next point I wanted to make. When we think about the issue of research under dire and emergency circumstances, we have to keep in mind that there are really different categories of people out there who could be the subjects of research. I just want to list three so that the subcommittee has them in mind as you think about the kinds of policy adjustments we might want to be making in this area.

First, we have competent people who face emergencies or unanticipated crises. In this group might be people who are otherwise competent, but who are rendered questionably competent by the

nature of a sudden accident, trauma, unanticipated onset of disease, or even the kind of coercive circumstances I just mentioned—do you want to donate a lobe of your lung?

These are people who may be rendered psychologically unable to give true and informed consent, maybe not by disease, but by lack of circumstances or time. So, that is one situation; subjects are competent, but time and circumstances make them dubiously incompetent.

Second, people who are never competent, they lacked competence to begin with. We have to deal with the fact that children, young adults, the mentally retarded, mentally ill—interventions are proposed for them under emergencies and dire circumstances, what should the boundaries be for people who have no prospective choice?

I guess in the third category, I would identify people who do face crises, but they can anticipate them. They may have competency; they know they are at risk of a heart attack; they know they have problems that might get them in trouble. As we try to weigh what sort of approach we want to take to consent and the oversight of research, we have to keep in mind that not everyone is in a situation where a crisis occurs out of the blue, but nonetheless they may be incompetent when that crisis happens.

So, we have different categories of people who we have to be thinking about. I am sorry to say that I don't think the regulations are sensitive to the different classes of subjects that exist with respect to emergency and dire circumstances.

Let me simply wrap up my oral remarks by a couple of comments about informed consent. It is clear that Americans want research to proceed to solve emergency situations and dire problems. I think it would be fair to say they don't want moral priggishness to stand in the way of making advances with respect to emergency technologies. They certainly don't want to see companies buried in paperwork requirements that don't serve any goal in terms of protecting subject rights or the dignity and welfare of people involved in research.

It also seems to me for some of the categories of people who I mentioned, informed consent won't work; it will not work. What must we do?

I think the answer is obvious. For some categories of research, if this society decides to allow it to proceed because it wants advances with respect to emergency treatment, the burden falls on the institutional review boards we have been talking about. The local committees at each hospital that exist to review research and to give approval both to the consent forms, and to the risk benefit ratio.

I would simply say that existing regulations for all categories of persons who face emergency circumstances are not adequate in terms of what these IRB's can do. They don't have consistent guidance, they don't have clear-cut rules, they don't have clear messages about what they are supposed to do. I am afraid they don't have the resources and manpower actually to bring it off.

We have heard one description already of an IRB made up of insiders within the institution who have the goal of seeing research

proceed being asked to step back and decide whether research can proceed.

It is a conflict of interest situation that is very acute, and when you don't have informed consent there, the individual's informed consent to mediate it may create a situation where you have got a fox guarding the chicken coop.

This is a little too disturbing to simply rely on that type of guardianship to do the risk benefit equations properly, so I would suggest this: What I think we need to do is, first, tighten the institutional review board regulation and institutional review board resources. We have to give people some resources to do the job locally that we want them to do in dealing with this tough category of research wherein informed consent isn't possible.

I think we need some specific guidelines on subject selection: Can children be involved at all? Can people who are mentally ill or people who are mentally retarded ever be put into this kind of situation? We need to have some sort of guidance about what sort of risk benefit equation for these special circumstances ought to guide research—minimal risk, fairly good evidence from animal and clinical studies beforehand, for example.

We need to make sure that those involved in the research have no conflict of interest. We haven't mentioned it yet, but some of these areas, the stakes in terms of profit and return to those who succeed, are high. Yet if people have ties of investment or stock or other types of arrangements, that may not be appropriate in this delicate area of research in terms of who is reviewing things, who is making judgments about where research should proceed.

I think we need to have something that was mentioned before, more audit function. I think there is a need for the Federal Government to make the occasional IRB audit. In the most delicate types of research, perhaps a special committee, a special review committee appointed outside local review to add an additional level of review.

What I have in mind here, if we are going to do emergency research on children, then maybe local review by the IRB isn't enough. Maybe that type of research should trigger a special type of review at the national level. Or, for large multicenter trials like the TIMI study. Maybe, we need more than just local review taking place at each institution. We may need some Federal oversight. The IRB's have to be held accountable. We have to have occasional visits to them to see what they are up to.

My intellectual guide on my left here, Dr. Katz, has convinced me that if IRB members do nothing more than stay in committee rooms and review informed consent forms, they won't be discharging their duty to the subject that they are supposed to protect.

Unfortunately, they don't often debrief subjects, and they don't often come after the fact to say what has happened and how are things going. That shouldn't be. There should be contact made with people who have been in research to see and follow up, to come to understand whether they feel harmed or hurt or whether other problems that weren't anticipated have arisen.

We can't let the struggle to find better ways to cope with unexpected emergencies and the sudden onset of ill health fall victim to moral priggishness, I agree with that. But neither should we

treat those who are rendered unable to consent by disease or circumstances just as objects. We still have to try to treat them as persons.

The best we can do to try and deal with this area is when we have to abandon a reliance on informed consent, either because it is imperfect, the people are psychologically vulnerable, or circumstances afford not much time to deliberate, is to beef up the oversight functions of the institutional review boards. They currently are too weak, they do not have the guidance they should, and they don't have the resources and composition they need, sometimes, to carry out their task in this area. That is the place I would suggest that the subcommittee press the regulatory agencies and Mrs. Shalala for action.

Chairman WYDEN. Dr. Caplan, thank you for a very thoughtful statement. What you have given us is just chock full of ideas that we really need to follow up on. I will have some questions for you in a moment.

[Mr. Caplan's statement may be found in the appendix.]

Chairman WYDEN. Let me tell you, first, I am very attracted to this idea of trying to set out some additional guidelines or standards for these institutional review boards. What is attractive about that is ultimately you still allow for a lot of local flexibility, a lot of local involvement, and at the same time you are not just saying the Government is going to take a hands-off, laissez-faire approach.

Let me also say that with respect to those conflict of interest rules, we have been working very hard with the National Institutes of Health to help them get out their conflict guidelines. We expect to have them early this summer, and we will be following up on that.

Finally, let me say that I very much appreciate your point that researchers are going to have to take a more hands-on approach and get out and talk with the patients.

I note Mr. Aller mentioned on several instances that what was particularly frustrating to patients was that nobody ever followed up with them. It was sort of like research remote control. Someone went off and did something once and then individuals and families had questions and nobody really had time for them. So, your point of being an advocate for folks in research trials is really well taken. We will have some questions for you in a moment.

Chairman WYDEN. I am glad you introduced Dr. Katz as really the intellectual mentor of this field. I know he has been working at this for many, many years. A lot of us have appreciated your leadership, Dr. Katz. Let's see if we can get you that microphone and if you wouldn't mind speaking right into it, that would be great.

TESTIMONY OF JAY KATZ, M.D., YALE LAW SCHOOL

Dr. KATZ. Thank you, Chairman Wyden and Representative Combest for inviting me.

I rarely testify before congressional committees. Indeed, the last time I was on the Hill was in 1974. But I couldn't resist your invitation, because I was struck by the emphasis you placed on consent and the protection of the basic human rights of research subjects.

That captured my imagination, because it is an issue that I have thought about a great deal during the last 30 years.

Before giving you a brief summary of the written statement that is before you, I have to digress for a moment and bring one matter to public attention. There was an error in the subcommittee staff report on human guinea pigs where it is claimed that the African-American males who were recruited for the Tuskegee syphilis study "were infected with syphilis." This is a quote from the report. This is not true. I was a member of the HEW advisory committee which recommended termination of the study in 1972, and I can provide proof that all of the subjects had contracted syphilis prior to their enrollment.

The violations of subjects' rights in this study were many, but deliberate infection with syphilis was not one of them, despite the widespread belief in the African-American community that it was. This belief has led to the conviction that by analogy physicians are now infecting African Americans with AIDS, a conviction which tragically may inhibit patients from seeking appropriate treatment. This matter deserves correction.

Now, a brief summary of my prepared statement.

Ultimately, in 1973, the Tuskegee Syphilis Study Ad Hoc Advisory Committee also made detailed recommendations on the regulation of human research. One of our major recommendations was the establishment of a National Human Experimentation Board. Senator Kennedy held hearings on a bill which he had drafted with my assistance that incorporated this idea. It never received the support of his colleagues in the Senate. But I continue to believe that such a board is needed. A piecemeal approach to human experimentation will not work now any better than it has in the past.

In 1973, we recommended that Congress should establish a permanent body with the authority to regulate at least all federally supported research involving human subjects. The board we suggested should be independent of HEW, now of HHS, for we did not believe that the agency which both conducts a great deal of research itself and supports much of the research that is carried on elsewhere is in a position to carry out disinterestedly the functions that we had in mind.

Your subcommittee's concern about research with mentally incapacitated patients, with unapproved drugs and medical devices illustrates the need for such a board. For in research with mentally incompetent patient-subjects in emergency rooms, we must confront a number of questions, and I will mention just three: DWC, how should the tensions between the inviolability of subjects of research on the one hand, and the advancement of knowledge, on the other, be resolved; two, can incompetent patient-subjects ever be recruited for the sake of science; and, three, if so, who should be invested with the authority to make such awesome, and they are indeed awesome, decisions?

For these questions to be answered adequately, they must be addressed in the context of overall guidelines for the conduct of experimentation with human subjects, and the deliberations concerning such guidelines must be conducted in a form and in a forum which allows for, and encourages, public scrutiny and hopefully the emergence of a national consensus.

These deliberations and ultimately the board, should at least remedy the following existing problems: One, at present, IRB's work in isolation from other IRB's and, thus, similar or duplicative experiments are being carried out at a number of different institutions with resulting exposure of an unnecessarily large number of subjects to research and research risks.

Two, the majority of IRB members are on the faculty of the institutions to which the investigators belong. This often makes it difficult for them to hold their colleagues to standards that will protect the subjects of research when such standards would create impediments for the conduct of research.

Three, local IRB's are under pressure, not only from investigators but from their own institutions as well, to approve research protocols. Academic institutions rely heavily on the revenues which accrue from the assessment of direct and indirect costs to the providers of grants.

Investigators are also under considerable pressure to recruit subjects as quickly as possible. Physician-investigators are the victims of institutional systems which penalizes them if in fulfillment of their ethical disclosure obligations toward patient-subjects, the pace of research is slowed.

Four, increasingly, research is being supported by pharmaceutical and biotechnical companies with economic rewards accruing to medical institutions and investigators. The conflicts of interest problems which such arrangements spawn are obvious and troublesome.

Five, these problems are now compounded by the proliferation of so-called freestanding IRB's, which operate outside institutional settings and from what I know are insufficiently regulated.

What concerns me, to begin with, is that these IRB's are for-profit enterprises, and that their owners appoint their own ethical review committees, the members of which are paid by the owners and serve at their pleasure. In such settings, conflict of interest is surely an ever present danger.

Finally, with reference to the idea of deferred consent, about which you have asked me, and presumably will ask me further questions, let me only state now that in my opinion and that of others, deferred consent, and I would add all its related forms, are best understood as not obtaining consent at all.

In conclusion, the importance of research has captured the imagination of the Western world. Human experimentation is now being carried forward on an unprecedented scale and with great expectations of the rewards it can bestow on mankind.

Yet, in the quest for progress, the danger is great that deeply held moral values of respect for, and the inviolability of, individual citizen-patient-subjects will be eroded.

This may be a price not worth paying, or it may be a price worth paying, but this is ultimately a question that you have to confront.

If, as some fear, a national board will slow the pace of medical advances by forcing society to make difficult moral choices in bright sunlight, and then perhaps making some research more time consuming to conduct, so be it. I am not convinced that this will happen, but if it does, I believe it is a far better option to embrace than our being corrupted by practices in secret. The recent revelations

about the radiation experiments are a telling example in point. Thank you.

Chairman WYDEN. Dr. Katz, thank you very much for an extremely helpful statement, and we will have some questions for you in just a moment.

[Dr. Katz's statement may be found in the appendix.]

Chairman WYDEN. Let's begin the questioning with the gentleman from Texas.

Mr. COMBEST. Thank you, Mr. Chairman. I think we all want to get to the same place. It is that difficulty of getting there where we don't create overburdensome Federal regulations but at the same time obviously protect the individual. That has got to be first and foremost, and yet we don't want to discourage or hamper research either. So, that is the challenge I think. Thank you all for a variety of testimony.

Dr. Caplan, I wanted to clarify something in my own mind, in part of your testimony and in the part that you mentioned verbally, the Ambu pump. In your testimony you had indicated that on page 2, and it is important to note that hardly anyone would find it useful or beneficial to use such a device which carries a much higher risk of restoring cardiac function than it does restoring neurological function. The Ambu pump would be used in substitute to CPR?

Mr. CAPLAN. Correct.

Mr. COMBEST. Would CPR be more effective in a neurological function than would the pump?

Mr. CAPLAN. Unknown. That is part of that research enterprise. CPR certainly does not work very well; we have heard that it only restores lifesaving function in about 15 percent of the cases. There is pretty good data that if it is not done rapidly, it is not going to restore any cardiac function at all. But, in one sense, that is part of the research enterprise. You are going to do more harm by having agents buy the better technology that restores heart function but still doesn't get that oxygen back to the brain in time.

Mr. COMBEST. But, and just again for my own clarification, are you contending that the Ambu pump would be less successful? While it might restore the cardiac function, that it would be less successful than CPR in restoring the neurological function?

Mr. CAPLAN. I think the more accurate way to describe it is CPR might not be very successful at restoring any function. The Ambu pump might be more successful at getting back heart function, but also might fail to restore neurological function. So, it would be better than what CPR offers, but carries this risk of creating these people who are kind of in a limbo.

Mr. COMBEST. Sure. But I need to—again, I need to make sure that I understand this. The function would be in a cardiac situation, the initial response I presume, I am obviously not a physician, would be to try to get the heart pumping, to keep the person alive.

Mr. CAPLAN. Right.

Mr. COMBEST. And that would be the main goal, and obviously the sooner that happens, the better the chances the person has neurologically to function appropriately as well.

Mr. CAPLAN. Right.

Mr. COMBEST. If given the option, here is the patient, if given the option of performing CPR or using the Ambu pump, in the cases

that the pump has been used, it has been proportionally more successful in getting the heart beating than CPR?

Mr. CAPLAN. For a small subcategory of patients, yes.

Mr. COMBEST. But it is used on much smaller numbers of patients at this point?

Mr. CAPLAN. Yes.

Mr. COMBEST. OK. Thanks.

Mr. Aller, I want to go back to your testimony, and there is a couple of questions I had about that. You said it in your testimony, I don't have it in front of me—what was the medication that you were given after you had signed the consent?

Mr. ALLER. Sir, it was Prolixin.

Mr. COMBEST. Is Prolixin now an approved medication?

Mr. ALLER. Yes, sir, Prolixin is an approved medication.

Mr. COMBEST. At the time it was not and it was the reason that you had to sign the consent in order to be able to be administered Prolixin.

Mr. ALLER. At the time, as far as I am aware, it was approved.

Mr. COMBEST. It was approved then?

Mr. ALLER. Yes.

Mr. COMBEST. Did I also understand you to say that there were a number of other medications that were available that were successful in returning—that would have returned—was it paranoid schizophrenia?

Mr. ALLER. Yes.

Mr. COMBEST. Back to a more normal life?

Mr. ALLER. Well, sir, there is a lot of variability in patients with schizophrenia. Some do well on some medications, some do poorly on the same medications. So, you really have to experiment with the dozen or so medications that you have that are approved, and they have been around for some time, and find out what works best for that individual patient.

Mr. COMBEST. Is Prolixin the medication which you use today?

Mr. ALLER. Yes, it is, sir.

Mr. COMBEST. In the consent form which you signed, you had indicated that there was one consent to administer and do testing in one area, but that the actual reasoning for the testing was something totally unmentioned to you, and that was actually to study the results of withdrawal of the use of the drug.

Mr. ALLER. Well, sir, there were two informed consent forms. The first was when I originally entered into the project in March 1988 and that was to receive Prolixin. The second consent form was the withdrawal phase of medication, and that was a misleading consent form. I don't have it in front of me. I have seen it, of course, but I don't have it memorized.

But the purpose of it was misleading. They didn't tell you they wanted to relapse, and observe you and relapse and then try to hospitalize you.

Mr. COMBEST. OK. But there was a second consent form relative to the withdrawal?

Mr. ALLER. Yes, sir. But it omitted foreseeable risks and alternative treatments.

Mr. COMBEST. I have not seen either that consent form or actually any consent form that would be used in this type of a method.

But is there any kind of open-endedness in this, in that while generally this is what we are attempting to do, there may be other things which we try to achieve in order to sort of leave an out?

Mr. ALLER. I would have to look at the language of the consent form, sir.

Mr. COMBEST. Do you know about—in this situation, it was not really a question of getting a consent form, it was what I would appear, assuming everything in here is a factual basis and we have no reason to doubt, it would seem to me that the problem was that there was a violation of that consent form?

Mr. ALLER. Yes, sir. It wasn't a proper consent form. It omitted foreseeable risks, alternative treatment. It didn't tell you, for example, that there are alternative medications, a dozen or so, for schizophrenia. There are different types of schizophrenia, and that if Prolixin doesn't work—for example, Prolixin didn't work for you and they didn't tell you that, well, you should try one of these other medications and we can try and see if that helps you. So, it didn't state that at all. It was misleading in that sense.

Mr. COMBEST. Do you know if the misleading consent form has legal remedies?

Mr. ALLER. Yes, sir. It is an action—I am not a lawyer, of course, but——

Mr. COMBEST. I thought maybe had you checked with one or something.

Mr. ALLER. It is probably fraud and intentional infliction of emotional distress, things like that.

Mr. COMBEST. So the question of whether in this case, even if we had regulations that determined—relative to consent forms, the same type of thing I presume could still happen in the future. The consent forms were not—if I understand it, a violation, and that could even exist in the future. I mean the problem which you encountered, even with additional Federal regulation, could exist.

Mr. ALLER. Well, sir, people do break the law constantly, and I don't mean necessarily in medicine, but in anything there are robbers, there are burglars.

Mr. COMBEST. Right.

Mr. ALLER. So I don't think that just because—I think there has to be an oversight board, like Dr. Katz said, to mandate that people are obeying the law of Congress.

Mr. COMBEST. Yes. That is exactly where I was headed with that, is that while we may set up all kinds of regulations or guidelines or whatever, that still doesn't necessarily indicate someone is going to totally follow those, or is not going to deviate or violate or move away from those. I, again back to Dr. Caplan's idea, I think that an idea of the—the Federal Government can get very intrusive into one's life, and can almost stymie progress if one is not careful.

I really like the idea of giving additional authority, letting that decision be made locally, or making for certain that the board is not a rubber stamp of the institution. Broader guidelines or whatever to, number one, ensure that these things are being done, that in the case that there is an actual emergency, that there is no other option, and possibly this is the only way.

I guess we all think if we are on our death bed due to a trauma, accident, or something, I mean, whatever they can pull out of the

hat to try, let's do it. In that case, we want to provide that opportunity, but we don't want to make it so burdensome that we can never attain that.

You all bring up some very interesting thoughts in this. I would hope that what we are able to do is to bring together all of this and get some guidance from NIH and from FDA. I would, Dr. Katz, hopefully it will be another 20 years before you find yourself in need to come back before the subcommittee. Kind of like a soap opera. About every 20 years is soon enough.

Mr. KATZ. I hope I will be kept alive by these unapproved devices.

Chairman WYDEN. All of you have given us excellent testimony, and I think you all understand it is not possible to just waive an ethical wand from Washington, DC, and magically produce a prescription that is going to deal with all of these unforeseen kinds of consequences.

But as you started off a couple of hours ago, Mr. Aller, there are certain basic kinds of ethical standards that are fundamental to caring for people and being an advocate for patients. I want you to know that at the end of the day we are going to make sure that the Federal Government puts in place rules that adhere to those principles.

You have performed a great service and I want to make sure that it is clear for the record that what you have essentially said is that before the research trials began, these individuals that you were talking about were essentially high functioning people; is that correct?

Mr. ALLER. There again, Mr. Chairman, there is a lot of variability in patients with schizophrenia. Some are attending colleges, getting good grades; some are unfortunately psychotic a lot of the time and need clozapine or some other type of drug, or if clozapine doesn't help them—so let's say a certain percentage of the patients are really high functioning, a certain percentage of the patients were average high functioning, and a very small percentage were not functioning.

Chairman WYDEN. Do you believe that you were adequately informed of the risks that were involved in the study you described today?

Mr. ALLER. Absolutely not. But I don't think—concerning the UCLA study, I was.

Chairman WYDEN. Do you believe that institutions like UCLA or the Government at this point have been protecting your interests as a research participant?

Mr. ALLER. Absolutely not. I wish they would.

Chairman WYDEN. So if a friend asked you to today whether you ought to participate in a study or give your consent even in one of these difficult, unforeseen circumstances, what advice would you give them?

Mr. ALLER. I would tell them not to do it, to run the other way and don't do it.

Chairman WYDEN. Mr. Palin, the restraints that you showed us, you brought these restraints here, did the hospital use them on intoxicated persons prior to the research trial?

Mr. PALIN. Yes, they did.

Chairman WYDEN. If restraints were used by the hospital prior to the trial, how did their use change after the trial began?

Mr. PALIN. Well, actually the change took place 5 months before when they changed the protocols. They used a brethalyzer instead of having blood drawn. Many, many patients violently opposed having their blood drawn, and one of the physicians worked with the committee in the emergency department to make some changes, and they wrote a new critical path, which happens to be exhibit B that I included within my testimony, and they changed the protocol to have a brethalyzer administered unless the patient was uncooperative or semicomatose. So, now we no longer had as big a problem.

When the study was instituted, they dumped the brethalyzer. They were no longer using it. Now every patient was going to have their blood drawn and it just created this violent situation.

Chairman WYDEN. Tell me, if you would, about this asthma study that involved children. Because I really found that very frightening. How did the Institutional Review Board come up with the idea that parents would want their children to gasp for breath in an acute asthma attack for an extra half-hour while the researchers worked?

Mr. PALIN. In my conversation with Linda St. Angelo, the director of nursing of the hospital, and Sandy Stamoulis, who was the vice president of services, they were making claims to me that this would be taking place very, very quickly from 5 to 10 minutes or less. Even that is too much, as far as I am concerned.

But the reality of the fact is Rhode Island Hospital's emergency department is the busiest emergency room in New England. They see 100,000 patients a year. It is very, very hectic, particularly in that period from about noontime until about 1 or 2 in the morning with sometimes 3 and 4 hour waits. Normally, a child who comes in with an asthma attack totally cuts by the wait. They are sent immediately to the emergent area to be treated with the nebulizing treatment. This is the way it has always been done. Because they have to treat them right away. It is a medical emergency. They bypass everything.

By instituting the study, now you have the wait. Now if one physician is in a room seeing a patient, isn't available right away, now the time lag starts to go in. After that physician is done, he has to go find the asthma doc, as they called him. Now, the asthma doc is not going to be waiting outside twiddling his thumbs waiting to go in and examine the patient, he is going to be with another. So, you have these delays that are taking place.

So, the physicians, it seems to me, went to the IRB saying very short wait, but in actuality and the reality of the case, it could very much be that half-hour timeframe. So, what the IRB saw I am not quite sure because the hospital refused to give me the protocol for the study and since I was in school, I didn't have the time to go after it with the Freedom of Information Act and actually get a copy of the protocol.

Chairman WYDEN. Is it your sense that the agenda of researchers to publish and promote each other is really highlighted by this asthma study where the interests of those researchers came before patient's rights?

Mr. PALIN. I think that in this particular case, absolutely, publish or perish argument really rings true. Because the physician involved with this study was a pediatric fellow, and what that is is you have got a residency period that the doctors serve and then after that they are trained in an area of specialization. It is a year or two training program. This physician is completing that fellowship timeframe. As a matter of fact, I think he completes it next month.

He had resumes out to many hospitals throughout the country, as many other fellows do. In many conversations that you hear that I have been part of within the department, because we worked very closely with the doctors, this area is very important. The hospitals, particularly the good teaching hospitals, want to see that the physician has been published, because they have joint appointments. They not only work for the hospital, they work for the university or college, the medical school. Additionally, within universities and colleges, it has been very important to receive promotions to be published. It has reached a point now to get the physician in the first place, you have to be published. It has become a real problem. We are starting to see research for the sake of research taking place.

Chairman WYDEN. So it would be fair to say that at this point you don't think these institutional review boards are being sensitive to the issue of patient autonomy or the principles of informed consent.

Mr. PALIN. No, I don't. Particularly at Rhode Island Hospital with the makeup of the IRB, it is very much a self-serving situation.

Chairman WYDEN. Let me just move on, only because we will probably be here until dinner time if we don't. But Mr. Palin and Mr. Aller, both of you have given us very helpful statements, and as I think I mentioned Mr. Palin was especially helpful in all of this in that you have seen and experienced this firsthand. That is the most valuable evidence that we could have.

Mr. Koepsell, if the informed consent question isn't settled, what is going to happen to your product and your company? The Government—we are going to have the folks from the FDA here in a little bit—if the Government can't move quickly to strike a balance between making sure patient's rights are protected and at the same time freeing you up from this procedural glue factory that you are stuck in, what is going to happen?

Mr. KOEPSELL. If there is no resolution to the informed consent issue, especially in the first responder market being ambulances, fire rescue, et cetera, there really isn't any way of doing a study in that area. Because that area makes up 70 percent of the patients that suffer cardiac arrest, then those patients will, number one, be potentially deprived of technology that could save their lives, and cardiologic would never be able to obtain that segment of the market, and therefore, we would not be in business. We would not exist without that potential market.

Chairman WYDEN. And how long essentially do you have the Federal Government hanging in abeyance like this?

Mr. KOEPSELL. At the present time, we have about another year and a half to hold this in abeyance.

Chairman WYDEN. You have a year and a half, but you have $7 million already into the product and how many years?

Mr. KOEPSELL. We have raised $5.9 million and already spent $2.5 million in developing the product and getting the IDE submission to the FDA. It will take us, if we start the hospital study and if, and again it is a big if, because we don't know if informed consent is going to work in this hospital study.

As I stated, many of the IRB's have already voiced their concerns about doing prospective informed consent on their patient population that gets admitted to the hospital to have 1 or 1.5 percent of them participating in the study. So, many of them are balking. If we cannot do the study even at the hospital level, we will be out of business within a year.

Chairman WYDEN. Your account is especially helpful, and let me say that I hear this kind of story from firms in the Pacific Northwest—I represent the State of Oregon.

So, we are going to do our best to try to make the system work for folks like yourself, and I especially appreciate your willingness to say that the patients come first. My sense is that there are a lot of companies out there like yourself who will frame it just that way.

My sense is with reasonable regulation, folks like yourself can do your business, and at the same time the rights of patients can be protected. Trying to find that balance is what we will be after this afternoon with the people at the Food and Drug Administration.

Mr. Caplan, let's move on to you, if we might.

At one trial site, according to the report of the Food and Drug Administration, several patients who had, "do not resuscitate" orders attached to their files were resuscitated anyway, with the device that I and Mr. Combest had been talking about this morning. Now, the trial had, as far as we can tell, no provision for informed consent. What are the bioethical issues in a situation like that?

Mr. CAPLAN. Well, that is an example of horrendous ethical violation. What those orders are is that someone has requested that they not have any resuscitation done on them experimental, standard, or otherwise, and it has taken us a while in this country, but we have succeeded in allowing the individual to control their medical destiny by using advanced directives, working out orders in advance, and trying to give guidance to physicians and nurses and others who treat them, even if they become incompetent.

There is no excuse for resuscitating anybody using any technique, experimental, therapeutic, or whatever if they have these DNR orders written on them. They wish no more attempts made to extend their lives using these technologies. So, it would be, one might say, the last place you would want to go to recruit subjects is off of the ranks of people who have DNR orders written on them.

I fear that because of this uncertainty about what to do when informed consent can't be obtained, we find subject recruitment going into places where it clearly should not, where it clearly should not be.

Chairman WYDEN. Well, we are talking about scary stuff, Mr. Caplan, and I appreciate your bluntly taking us through it.

We want to ask you about yet another trial. The same device I might add, again, without the requirement of informed consent

being part of the protocol. The approved institutional review board protocol allowed use of this device in children as young as 8, according to the files at the Food and Drug Administration. Again, and in connection with the protocol, that doesn't demand informed consent.

What is your sense about the special implications of using children as they did in this circumstance?

Mr. CAPLAN. Well, sadly children, too, can undergo dire and emergency circumstances, fall in a swimming pool, have a head injury, car accident, et cetera. They may need to face the choice of techniques intended to help and benefit them.

As we have heard with the asthma study, certainly the standard that we want to see followed when a child is involved is that the most careful research is conducted on all of the available groups before we decide to withhold something from a child, whether it is standard asthma treatment, standard resuscitation treatment or whatever.

So, my argument would be when children are involved and informed consent can't be obtained from them, by definition, and proxies may not be available to do it, that may be one of the places where local review isn't enough. We may need to set up a special committee of oversight. Emergency research on kids is about as delicate and difficult a thing as we could ever imagine. We have got to have extra oversight there.

We want it to proceed with all efficiency. We want to proceed with all proper speed to let these kids get a shot at things that might help them, but local review may not cut it. They need someone to step in, I would think maybe outside the institution, maybe at the national level, who can say we have special standards here, maybe even an organization that isn't part of the HHS, to step back and say we have to give this extra scrutiny because we have kids involved.

I can't imagine anything that is more ethically sensitive than unconsented research on kids. To hear that it has taken place without any provisions being in place is just sad.

Chairman WYDEN. Now, the subcommittee recently received a letter from an advocacy group in New York, a group that represents the mentally ill. This letter was written by a Bronx VA Medical Center psychiatrist explaining why doctors in a trial designed to gauge the effects of weening mentally ill persons from their medication failed. It is a matter of the trial's design to inform those persons that withdrawal from their prescription could lead to relapse or that their psychosis might worsen. Instead, in this instance, the final version of the consent form stated that drugs would be restored if subject felt that their old symptoms might be returning. The doctor said that this language was chosen so as to "not cause unnecessary anxieties and therefore would not be in the best interest of the patient."

Again, what would be your reaction to this kind of situation which has been brought to the attention of the subcommittee?

Mr. CAPLAN. Inexcusable. The local IRB should be able to handle that and make sure that every prospective subject has full and complete information about options and about all side effects. That

is standard requirements under existing informed consent regulations.

I must note for the Chair that for some time now I think we have been waiting for local IRB's locally to get some guidance about regulation of research involving the mentally ill. That has not been forthcoming. There are no special regulations issued. The kinds of stories we have heard about the schizophrenia study with the relapse and so on, the one you are describing, these make me feel that if the local IRB's are really going to be able to do their job, they may need some special regulations making sure that people get all the options, understand that they don't have to participate if they don't want to, and that people aren't being paternalistic about withholding information from them based on some such excuse as inducing anxiety.

That is a group that probably has experienced a fair amount of anxiety already. It wouldn't come as a shock to them that there are more things they might face that will carry risk.

Chairman WYDEN. Some say that the Institutional Review Boards are really fraught with conflicts of interest. Is that a judgment that you share?

Mr. CAPLAN. I do. I think that there are problems with Institutional Review Boards. Dr. Katz has mentioned the fact that frequently they are composed of people who are colleagues of the researchers. It is hard to go to work every day and tell your colleague you don't want them to do something or you want to interfere with their ability to get a grant or get a promotion or publish a paper.

When I was in New York at Columbia University and on the IRB at that institution, I was the person representing Harlem community for 3 years. There might have been some gap between my ability to represent that particular minority community in that location and my being selected as the community representative! There are problems with how we pick who serves on IRB's, with what their ties are to the medical industry, to the research community, and as I have noted, with too vague instructions about how to bring this off and I have to put in a plea, too, with no fiscal support. These are basically run as overhead operations.

If they wanted to audit, if they wanted to bring subjects in, if they wanted to do anything, they have no fiscal resources to do any of this. In some ways, then, they often act more as a rubber stamp or a tunnel through which research passes quickly, but, they don't do the job that one would expect them to do locally of holding researchers to account.

Chairman WYDEN. You raised an interesting point regarding different degrees of ethical risk or danger depending on the kind of individuals involved. I think it suggests that individual groups might or should be dealt with differently according to any procedures for obtaining consent or seeking exception.

Could you tell us, if you would, how you would assess these various groups and how the Government might go about setting in place a set of standards to incorporate this idea of differing nature of risk?

Mr. CAPLAN. Well, there are different classes of people who face different sorts of problems and crises. I mentioned, for example, there are some people who know that they are at risk of a heart

attack, who know they are at risk of an asthma attack who are competent.

We could lay in procedures and say for that group, with the anticipated circumstances, prospective consent is possible and you wouldn't have to fish through the entire patient population of the Nation to find the subpopulation that is going to need the technology. Sometimes you can identify them in advance.

For children you may say if it is anything more than minimal risk and in emergency circumstances it is going to have to go up to a national committee, they must realize informed consent is impossible and that is going to have to have standards applied that show real likelihood of important benefits, not minor research, not small stakes research, but serious consequences like the therapeutic benefit based on tough animal trials, lots of clinical work before you do such research with a child.

Let me add one other thing about how one might sort of scale different types of research for IRB's to look at. It is my belief that the IRB's now are swamped because they review everything, whether it is a blood draw for certain kinds of studies or working with someone who has a mental illness or a child looking at the prospect of an emergency intervention for a head injury or something like that; they all come to the IRB.

One of the things that I have suggested for some time is maybe we want to let the IRB's be a little more selective in what they review locally. Maybe there are some things that are minor, minor risk can be waived off or exempted or just go through without all the paperwork being done. Maybe there are other categories of research where you have to be in there and we put in a "debrief the subjects" requirement after the fact.

Now, it is almost that pile of paper on the corner of the table might be what the average IRB sees at an average meeting and there may be ways to streamline that process, we could make it more of an audit system rather than trying to make sure every time somebody got a research idea, it shows up at the IRB.

Chairman WYDEN. We will follow that up with you because I think you are saying that not all of these research procedures can be put in a cookie cutter, and that not all ought to be treated equally; that there are some riskier than others, and I think that is an innovative suggestion you make. The only other point is about the matter of deferred consent, being an alternative to informed consent.

We talked to folks at the FDA and they don't know about such a creature. They don't know about something called deferred consent and have essentially said that in their view it doesn't exist. Why don't you, if you would, define it for us and tell us if you think this kind of thing ought to be allowed?

Mr. CAPLAN. Deferred consent is the version of time travel where you come backwards from the future and go into the past and let someone know retrospectively that they have been a subject and is it all right with them. It clearly is a concept that doesn't hold up. It is not coherent.

I do believe that minimal decency requires telling somebody after the fact that they have been in a experiment. If that has happened to them, there is a duty to disclose that. But as far as its effective-

ness is concerned, in my opinion deferred consent is not a concept that is meaningful.

Chairman WYDEN. That is an important point. You compare it to time travel. I think what Mr. Aller and others are saying is compared to time travel given these kind of abuses, some folks aren't coming back. I appreciate your laying it out bluntly like that.

Let me go to you, Dr. Katz. The Office of Protection From Research Risks recently sanctioned the University of California, Los Angeles for a trial involving subjects with mental illness. The primary issue seemed to be a lack of sufficient information about the scope and hazards of the particular trials.

I think the subcommittee would be interested in knowing your views on this action and whether or not you think the situation at UCLA was really just an anomaly, a rare occurrence, or was it in fact, more representative of a larger pattern?

Dr. KATZ. No. That is just a problem with the UCLA study and the UCLA IRB. What the UCLA IRB did is not an anomaly. I have many examples from other States, including Texas, and Wisconsin, where the IRB has approved similar questionable research studies. I submitted to you my University of St. Louis law review article. In it I give an analysis of certain aspects of the UCLA study, focusing primarily on the research protocols submitted to the IRB, and also the informed consent form eventually signed by the participants.

By the way, the review of informed consent forms is one of the major functions that IRB's perform. The UCLA informed consent form was grossly deficient in all kinds of ways and Mr. Aller referred to some of these deficiencies. Also the research protocol itself, submitted to the IRB for review, should have been much more carefully scrutinized and further explanations required of the researcher.

One that immediately comes to mind was the monitoring of the research subjects if they should relapse into schizophrenia. There was nothing in the research protocol or hardly anything that indicated the care the researchers would be taking in monitoring the subjects, once the first symptoms of schizophrenia would manifest themselves. I am not suggesting that they didn't do so. I am only suggesting that as a reviewing body, they had to ask for much greater specificity of the monitoring process.

Chairman WYDEN. Let me ask you as well, Dr. Katz, about the situation at the Bronx VA Medical Center that I asked Dr. Caplan about. This was a situation where the doctors in the trial designed to gauge the effects of weening a mentally ill person from their medication as a matter of the trial design failed to inform the persons that withdrawal of the medication could lead to relapse. The consent form simply stated that drugs would be restored if the patients felt their old symptoms were returning.

Dr. KATZ. Again, if this were an isolated incident, one might forget about it, but it is not an isolated incident and I have written about it at length. Look at the two statements that you quote from the justifications of psychiatrists. "The drugs would be restored if the subjects felt that their old symptoms might be returning."

Next sentence. "It would cause unnecessary anxiety and therefore would not be in the best interest of the patient." Suddenly we

move from subject to patient. These are research subjects, but now they are being treated as patients.

I think inferentially that the researchers here invoked the therapeutic privilege, which is a questionable privilege in a therapeutic situation, but has no relevance to the research situation. It does not exist, therapeutic privilege, in law for research practices.

Also, if subjects felt that their old symptoms might be returning, that is not something for subjects to evaluate. It is for physicians to evaluate and to assure us that they would do something if symptoms were returning.

I could say more about it, but let me say one more thing about this and I have heard it again and again and again. The doctor said this language was chosen so as not to "cause unnecessary anxiety and therefore would not be in the best interest of the patient."

Two things. If it causes such anxiety in research settings, don't do the research with these patients.

Second, my speculation is the person who is anxious is not so much the patient but the researcher, who has to look at patient subjects straight in the eye and say I want you to participate in a research project where your old symptoms will recur. Will you give permission for participation in such a project?

I am not saying that such questions shouldn't be asked, but I raise the question who is anxious here, the investigator who has to make these kinds of disclosures or the patient subject who receives them.

Chairman WYDEN. I think you make a very important point. It seems almost as if the research subject's status is a matter of convenience.

When they want to call them a subject, they will call them a subject. When they want to call them a patient, they call them a patient. But it seems as if the characterization is based essentially on what is convenient for researchers and investigators and that is not my definition of a policy that protects the rights of patients in our country.

Let me ask you about the drug fialuridine, FIAU, considered a promising drug for treatment of hepatitis B, a disease that afflicts something like 300 million individuals worldwide. This drug was the focus of trials at NIH, Children's Hospital in Seattle and the VA in San Diego, but the drug's liver toxicity was not known until after 5 of 15 patients taking the drug over a 4-week or more period died. The case was described by the Food and Drug Administration as being one of the worst catastrophes in recent history with respect to experimental treatment.

The agency earlier this month admonished four doctors involved as researchers. Apparently one of the problems, according to the FDA letters, was the failure of scientists to get proper informed consent. It seems again that we are talking about children, again talking about tragic consequences, again talking about cutting corners with respect to informed consent. What is your assessment based on what you know?

Dr. KATZ. I know a little bit about the study. By the way, footnote 11 in my article makes some comments and describes the study at some length.

There are questions here about—actually, in my view, the informed consent form was quite good with respect to alerting subjects to the risk of participating. What the informed consent form did not do is to be quite straightforward about the fact that this was a research study.

The well-known bioethicist Judith Swazey said that they should not have called it a new medication which is a term of art again often used, but they should have made it quite clear and in some detail that this was an experimental product that was being tried out in order to test its effectiveness in hepatitis B.

That was not done, and that is a very common problem in many informed consent forms that I have read; that the issue becomes new medication, a study, when it is not that at all, but it is an experimental intervention and patients have to know what an experimental intervention is, that an experimental intervention is not the best possible treatment available to them today, because patients often believe this, but an experimental intervention means that the interest of the patients will have to be subordinated to some extent to the rigors of the research protocol.

Finally, I think the FDA exaggerates when it says this is the worst catastrophe in recent experimental history. Of course it is tragic that 5 patients died as a result of this experiment. But in focusing on that issue, we do forget, which I think should be our greater concern, namely the inattention investigators pay to disclosure and consent.

Finally, I want to say something about what Representative Combest said earlier. Of course, there are many times that informed consent may not be possible, and that is true and we have to face up to this. But we must not allow institutional review committees to make judgments about when informed consent can be dispensed with. They do not have the authority. They do not have the capacity. They do not know enough about law and the great value in our democratic society that we place on disclosure, consent, autonomy—we hate compulsion, we even have difficulties of agreeing fully that there should be a compulsory draft.

You remember the debates in Congress on that subject, and here we are asking people to be compelled to participate in research without their consent. That is an awesome request. I do believe at times that request has to be made, but that is one of the major reasons why I asked for a national body, because only a national body and ultimately with your approval, Congressman Combest, can such violations of democratic rights be tolerated for the sake of science.

Chairman WYDEN. I am glad that you characterized the informed consent situation in the fialuradine trials as one where informed consent was not offered in a straightforward way, because that is certainly more precise than I was. But I think it makes the central point that concerns me. Here you are talking about children.

You are talking about subject candidates that cannot comprehend and it seems to me that is not an example of the kind of informed consent process we want, where investigators are being less than straightforward with children. I appreciate your being specific about that.

Let me ask you also about the matter of investigator conflict of interest which you talked about as well in your statement. Is it possible that you could give us some anecdotal or hypothetical examples of what you might be talking about in that situation?

Dr. KATZ. Let me give you one not such anecdotal—such hypothetical, but let's consider it for these purposes a hypothetical example. A medical device company wants to test a new surgical instrument for a very common surgical condition that if it proves to be successful, would be a great advance and very, very profitable for the institution. Of course, the company wanted these results, these experiments done as quickly as possible. It was possible to make certain shortcuts in the research protocol that one—that good researchers even would have debated, is it a good shortcut, is it not a good shortcut.

These are still very—will it jeopardize the results or will it not, still in the light of medical uncertainty, still unresolved issues. It was decided in favor of making these shortcuts, but the investigators had bought stock in the company, some members of the IRB had bought stock in the company and one of the major university hospital staff, knowing about what was going on, had bought stock in the company.

Now being also a psychoanalyst, I believe that our unconscious can play all kinds of tricks on us, and we are not fully in control of our unconscious functioning. It is just too tempting under these circumstances to rationalize shortcuts on the basis of the need to send your children and grandchildren through college—it is very expensive these days.

Thank you.

Chairman WYDEN. Let me ask you one other question if I might. We have not looked at the matter of unconscious functioning. That might be a phrase people might apply to the way some of us vote from time to time around here.

The only other question I had dealt with this new development you talked about with respect to freestanding Institutional Review Boards, which I gather is a fairly recent development. What kind of oversight do you think would be appropriate to apply to freestanding Institutional Review Boards?

Dr. KATZ. First of all, Chairman Wyden, I hope you and another committee can really look into the matter and for you to ask the FDA to give you an accounting of how many of these freestanding IRB's exist, how they function. From just looking at the regulations, they are not regulated very well, and I cannot at this point give you any detailed recommendation but it seems to me to be—after all, Washington is now full of conflict of interest kind of discussions, that there is a conflict of interest when the owner of a for-profit freestanding IRB appoints his or her own ethical review board, pays a salary to the members and can discharge them at his or her pleasure.

Moreover, a second issue, you mentioned it in some of the comments you sent to me, namely IRB shopping. My expectation would be, though I don't know, that probably IRB shopping is much more rampant with freestanding IRB's than it is in university IRB's, but there are some problems there, also. You find the IRB that—where

the chances of approval are great and drug companies in particular make use of these freestanding IRB's.

In one conversation I had with a very thoughtful person who owns such an IRB, he said that, yes, we will of course try to make modifications in the research protocol, but it is too delicate to turn any of them down because then maybe that company will no longer come to us.

Chairman WYDEN. And these freestanding Institutional Review Boards are essentially regulated by no one?

Dr. KATZ. There are, and again I haven't looked at the regulations for a year and you might ask when the person from the FDA is before you, but from looking at the regulations last year, they are very minimal and really don't address the essential issues.

Chairman WYDEN. Let me yield to the gentleman from Texas.

Mr. COMBEST. I had one more question. We have a saying in Texas that I don't have a dog in that hunt, which I don't. I don't have a bias in this one way or the other. We are just trying to find out the total details so we can come up with hopefully some positive suggestions.

I am looking forward to some of the other witnesses. I wanted to read specifically a part of a testimony of Dr. Rockwell to Mr. Aller and ask you a question.

Dr. Rockwell from UCLA indicates, I am operating under severe ethical and legal constraints. If this constraint was removed and I was able to describe to you the specifics of some individual patient cases in the study, the picture would become abundantly clear. The subcommittee would see that these outcomes were indeed not the result of the lack of documentation of informed consent study or of the design of the UCLA study. We are not able to discuss the specifics of a patient's medical records without the permission of the patient. The patients and/or their families have so far refused to grant permission to discuss their cases.

As a result, they have essentially created a de facto gag order for UCLA, giving rise to the situation where patients of families can give their version of what happened, but the UCLA doctor is not allowed to do the same. This unfair playing field has resulted in broad publication of many inaccuracies and misunderstandings about the UCLA study without the opportunity for rebuttal.

Mr. Aller, I would just ask you—did UCLA request permission to use the specifics of your case?

Mr. ALLER. On a number of occasions they have, but they are under no confidentiality. Our attorney has advised us that because we and another family are suing them, they are free to discuss the case.

Mr. COMBEST. They are free. So, you have not refused UCLA's request to use information in your specific case?

Mr. ALLER. Well, we don't want to sign a waiver because then if they say something that is not true we can't take any action against them. But they are under no constraints to talk about our case because it is under litigation.

Mr. COMBEST. So anything which you had stated relative to your case could be rebutted with no problem as far as you are concerned by Dr. Rockwell?

Mr. ALLER. Because of the lawsuits, they are under no confidentiality.

Mr. COMBEST. Thank you.

Chairman WYDEN. You have been an excellent panel. A lengthy panel, but well worth it, with many very useful suggestions. We will excuse you at this time.

Chairman WYDEN. Our next panel is Gary H. Briefel, M.D., chairman, Institutional Review Board, Johns Hopkins Bayview Medical Center, Baltimore, Maryland; Wesley M. Todd, M.D., Director, Medical Affairs/Product Strategy, The Upjohn Company; Donald Rockwell, M.D., director, Neuro-Psychiatric Hospital, UCLA Medical Center; Michelle Biros, M.D., Hennepin County Medical Center, Minneapolis; Norman Fost, M.D., professor, Department of Pediatrics, University of Wisconsin Medical School.

Gentlemen, we welcome you. We thank you for your patience this morning through a very lengthy panel.

It is the practice of this subcommittee to swear all the witnesses who come before the subcommittee. Do any of you have objections to being sworn as a witness today?

Please rise and raise your right hands.

(Witnesses sworn.)

Chairman WYDEN. We will make your prepared statements a part of the hearing record in their entirety. If you could take 5 to 7 minutes or so to highlight the major concerns you have, in the interest of time that would be helpful.

Let's begin with you Dr. Briefel.

TESTIMONY OF GARY H. BRIEFEL, M.D., CHAIRMAN, INSTITUTIONAL REVIEW BOARD, JOHNS HOPKINS BAYVIEW MEDICAL CENTER, BALTIMORE, MARYLAND

Dr. BRIEFEL. I would like to thank Congressman Wyden, his staff and the other members of the subcommittee for inviting me to speak on the role of IRB's, particularly as they relate to the review and approval of emergency room research. My comments today represent the views of the two IRB's that serve the faculty at the Johns Hopkins University School of Medicine. The following is a summary of our written responses to the questions posed to us by the subcommittee.

Although I have been serving on the IRB for more than 10 years, my major responsibility is treating patients with kidney diseases. My commitment to serving on the IRB stems from my interest in keeping up with new developments in medical research, my general interest in medical ethics but, most importantly, my firm belief that IRB's perform an important service to subjects and researchers.

The writers of the Belmont Report recognized that "investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards and suggested that others who are independent of the research share in the responsibility." Hopkins IRB members understand that their major role is to protect subjects and are fully aware of the historical precedents that have led to the establishment of IRB's. Research protocols submitted to our IRB's undergo careful reviews by the full membership of the Board which, in addition to scientists

with a broad range of expertise, include two lay members who are unaffiliated with the institution. Considered in the analysis of the protocols are judgments of the scientific value of the research, the design of the study, the abilities of the researcher, the characteristics of the study population and the risks to the subject relative to the anticipated benefits.

Since in research, as opposed to clinical care, the benefits often accrue to society rather than the individual it is important that the subject decide, through the informed consent process, whether they want to participate and accept the risks. For these reasons, IRB's pay particular attention to the content of consent forms and the circumstances under which consent is obtained.

In the ideal world, subjects would have sufficient time to read and understand consent forms, ask questions of investigators, consult trusted individuals and this process would be unhindered by stress, emotion, or cognitive impairment. This ideal scenario frequently conflicts with reality when research is conducted in the emergency room setting. The writers of the Belmont Report and the Federal Regulations recognized that it would be necessary to perform medical research on individuals with diminished autonomy and included guidelines to help IRB's decide when such research could be ethically performed.

Some of the most difficult protocols which we have to review are those for which a waiver of consent is requested. These studies are extensively discussed and are only approved when we are convinced that they cannot be done in any other way and the subjects are not exposed to significant risk itself. We would like to counter the notion that this kind of research is common. At least in our institutions only two protocols out of more than 1,000 which were reviewed in the past 2 years qualified for waiver of consent in emergency room or critical care settings. Hopkins IRB's do not accept the concept of deferred consent since it is not possible to obtain consent for something that has already occurred. We limit the waiver to research protocols that meet the DHHS criteria. We agree, however, that the definitions need further discussion and clarification. For example, the definition of "minimal risk" is often debated by IRB's. We believe that the definition should be broadened. It makes sense to judge risk relative to that which individuals are already exposed associated with their illness. We would also suggest that guidelines similar to those employed for the study of children should be adopted which would specify the types of emergency research that can be approved if they involve more than minimal risk. It should be recognized that no matter how tightly the regulations are written, there must be some flexibility allowed for IRB's to interpret and apply the rules. The fact that some IRB's apply or interpret the rules in slightly different fashion does not lead one to conclude that one position is ethical and the other is not.

We are pleased that this subcommittee has taken an interest in this issue since IRB's have been struggling with it for years. The topic of emergency room research and the consent waiver issue were intensely debated and discussed at a national meeting that took place last year and was attended by IRB members, researchers, ethicists, lawyers and members representing the pharma-

ceutical industry, Government and the public. We believe that it is essential that the public retain trust in the doctors who perform medical research and that trust can only be maintained if potential subjects feel that advantage is not being taken of their trust. The IRB review process is an important part of the mechanism that has preserved the public's faith in medical research and may explain the extraordinary absence of legal suits relating to medical research much as opposed to what is seen with clinical care.

In conclusion, there are a limited number of research studies performed without waiver of consent. We recognize that this is not a justification for performing this kind of research since there is no societal obligation for being a research subject. We believe, however, and there is evidence to support the contention, that the American public strongly desires improvements in medical care and are willing to assume the risks associated with this progress. Under the conditions that I have just described, and are presented in more detail in our written testimony, we believe that there is good reason for this kind of research to continue under close supervision by IRB's and perhaps Ethical Advisory Boards. We hope today's hearings will result in better guidance for IRB members and investigators, as well as help the public become better informed.

Chairman WYDEN. Thank you. You have been very helpful and you were also very brief while being very helpful.

[Dr. Briefel's statement may be found in the appendix.]

Mr. BRIEFEL. I tried to follow the rules.

Chairman WYDEN. Dr. Todd.

TESTIMONY OF WESLEY M. TODD, M.D., DIRECTOR, MEDICAL AFFAIRS/PRODUCT STRATEGY, THE UPJOHN CO.

Dr. TODD. I am Wesley Mark Todd. I am a physician with specialty training in neurology. I have trained in clinical research and have been directly involved in various aspects of clinical research for more than 10 years. I have been a subject volunteer investigator, medical monitor, a member of an Institutional Review Board and director of a clinical investigation unit. Currently, I am director of Medical Affairs Product Strategy at the Upjohn Company.

Upjohn was invited to testify today because the company is currently developing an experimental emergency treatment called tirilazad mesylate. This drug is being tested in people who suffer subarachnoid hemorrhage, ischemic stroke, head injury or spinal cord injuries. All of these are devastating medical conditions with few or no current treatment options.

The purpose of my testimony is to elaborate on several key points that relate to the participation of people in biomedical medical research and to a pharmaceutical company's ability to develop new medicines for life-threatening diseases.

The first point is that the autonomy and safety of volunteers and the integrity of the scientific research are the most important aspects of Upjohn clinical trials.

Second, the development of new therapies depends upon patients who volunteer for clinical studies.

Third, the development of life-saving medicines for various serious medical conditions depends upon an exception to the traditional prospective informed consent. Without such an exception,

important lifesaving medicines cannot be developed as effectively and efficiently and the availability of new treatments may be significantly delayed.

Before I elaborate on these statements, the Upjohn Company acknowledges that the participation of human volunteers in medical research poses complex, ethical, social, legal and medical issues. As a result, the subject should be discussed openly and often and in forums where a diversity of nonscientists and scientists are represented. Upjohn values meaningful prospective informed consent as a foundation of ethical medical treatment and research. It is a goal toward which physicians and Upjohn continually strive.

The company's objective is to ensure that informed consent is a two-way conversation that respects the autonomy of the individual. This conversation between the investigator and the potential research volunteer must make clear to the volunteer that he or she is being asked to participate in an experiment. Risk must be stated. In this conversation, the investigator has an obligation to listen to the concerns of the volunteer and to encourage him to express his understanding both of the experiment and of his rights as an autonomous individual. Meaningful prospective informed consent requires time and the ability to understand and communicate.

One of the issues germane to this hearing is under what circumstances and according to what parameters should exceptions to informed consent be granted. For example, what alternative procedure to prospective informed consent should be implied in an emergency room setting when a patient is unconscious and the time for treatment is short? On this issue, the Upjohn Company would make three statements.

First, we acknowledge that the question of how to conduct research in emergency situations when patients cannot understand or communicate is one of the most challenging questions facing those interested in the ethics of clinical research.

Second, in some cases exceptions to prospective informed consent should be made.

Third, in these cases a prescribed process should be followed prior to the commencement of the experiment. Clinical investigators who write protocols must evaluate and confirm the circumstances that require exception to informed consent, and they must formulate an ethical process to secure such exceptions. This procedural alternative to prospective informed consent must be reviewed by the FDA and by the Institutional Review Board.

Both the FDA and the Institutional Review Board have the authority to reject, modify or approve the protocol and its informed consent procedures. Upjohn clinical investigators rely upon the FDA regulations that specify the conditions for valid exceptions to prospective informed consent. Upjohn acknowledges the efforts of the FDA on this issue and agrees with the FDA on the conditions for exception to informed consent specified in 21 CFR 50.23. Upjohn believes that experimental medicine must have a favorable safety profile. These conditions characterize our studies of tirilazad in head-injured individuals.

Head injury is a life threatening and seriously debilitating medical condition for which no effective treatments exist. Many head injured individuals arrive at the emergency department unconscious.

Continuing analysis of safety data shows tirilazad to be safe and well tolerated. Experimental evidence suggests that tirilazad interferes with the destructive biochemical process that occurs within the first several hours after head injury. For this reason, the head injury study protocol calls for administration of the first dose within 4 hours after injury.

This short time period for the drug administration, the safety profile of the drug, and the patient's imperative state of consciousness as a result of the injury together establish the need for exception to informed consent. The decision to enroll an unconscious injured patient in the study is first sought from the patient's family. If a family member cannot be located, the decision to enroll the patient must involve a physician who is not participating in the head injury study.

If exception to informed consent is granted, the enrollment of the patient is communicated to the patient's family immediately, and to the IRB within 5 days. As soon as a family member is located, the informed consent conversation proceeds. The family member has the authority to decide if the patient continues in the study. If the patient regains the capacity for making informed consent, the informed consent conversation occurs and the patient may choose to continue or discontinue study treatment.

A word about IRB's. IRB's are the vital guarantee of ethical conduct in human research. Upjohn believes that IRB review of medical research works with great efficiency and that it is a unique and effective system for evaluating the ethical issues of clinical research and for assuring the autonomy and safety of human subjects.

There are few subjects more deserving of soul searching than the participation of vulnerable patients in clinical trials. Such searching and the movement toward a consensus that will be forever dynamic will aid the development of lifesaving medicines for head injury and other serious medical conditions. Upjohn welcomes the reevaluation of medical policies to identify better procedures to ensure appropriate protection of the autonomy and safety of patients and to ensure protection of development of experimental life-saving medications.

Thank you for inviting us to participate in this discussion.

[Dr. Todd's statement may be found in the appendix.]

Chairman WYDEN. Thank you very much and I will have some questions for you in a moment.

Dr. Rockwell, welcome.

TESTIMONY OF DONALD ROCKWELL, M.D., DIRECTOR, NEUROPSYCHIATRIC HOSPITAL, UCLA MEDICAL CENTER

Dr. ROCKWELL. Thank you, Chairman Wyden and members of the subcommittee.

My name is Don Rockwell, and I am submitting this testimony on behalf of the University of California, Los Angeles. I am the director of the UCLA Neuropsychiatric Hospital and have practiced psychiatry for the past 27 years.

I have a particular interest in matters related to research and informed consent, having served as a chair of an Institutional Review Board at another major research institution, and having taught

medical ethics. The protection of human subjects in medical research is a crucial issue that you are addressing this morning.

I am pleased that the subcommittee is addressing this area, since it is both complex and continually evolving. It merits an open and full discussion among researchers, patients, subjects, legislators and regulatory agencies. Working together, these groups can make further improvements in the protection of human subjects in research, while avoiding simplistic, quick-fix changes that could—despite the best of intentions—ultimately set back the development of improved treatments for disease.

Over the past 3 years, the UCLA schizophrenia study has been under review by the Federal Office for Protection from Research Risks, which was investigating allegations regarding informed consent made by some family members of patients in this study. UCLA has fully cooperated in this comprehensive review.

As a result of the OPRR review, UCLA is making several changes in documenting its informed consent and review process which are described in considerable detail in my written statement. For the sake of brevity, we will not repeat that here.

As was mentioned earlier, I am constrained in terms of talking about patient-related information, despite Mr. Aller's verbal comment that I could. Unfortunately, we need written informed consent to be able to talk about his particular clinical situation, and we do not have that at this time.

I would like to address four questions on the UCLA schizophrenic study. This is a study of psychiatric outpatients using drugs available currently in the psychiatric community. What is the purpose of the study? The purpose of the study is to understand the 1.2 million Americans who are suffering from schizophrenia. There is a great deal known about the later stages of the disease, but a great deal about the early stages is not known.

Schizophrenia is an absolutely devastating disease, not only to the patient, but to the patient's family, as well. It is usually recurrent despite the best treatments available. The goal of the UCLA schizophrenia study is to improve diagnosis and treatment of schizophrenia by understanding more about the development of the disease and factors which may help predict its course in individuals.

Better identification of factors that make some individuals more prone to schizophrenia and to schizophrenic relapse should help us develop preventive intervention strategies in the future. Around the country, most research to date has studied chronic, long-term schizophrenic patients, whose course of disease and need for medication is better understood. Relatively little is known about patients who have recently had an initial psychotic episode.

There are many medications that are commonly prescribed to minimize the symptoms of schizophrenia. Each has significant drawbacks that limit its effectiveness. All the drugs in our studies have been fully approved.

There is a wide variation among patients and their degree of recovery during the years after an initial episode of schizophrenia. For patients who are doing well, it is not clear to physicians how long to continue ongoing outpatient medication, which involves risk of side effects. We know that perhaps as many as 20 percent of the

subjects will not need to be on medication. We just do not know which subjects they are.

Because of the above-mentioned problems with medication and because of the variability among patients, it is common clinical practice worldwide for doctors to give patients periods without medication during the initial years after the onset of schizophrenia. These periods need to be closely monitored, since some patients do well without medication and others do not. One of the specific goals of the UCLA study was to identify factors that predict the need for short-term outpatient medication versus long-term continuous medication, the key issue in the treatment of the early stages of schizophrenia.

The treatment protocol in the UCLA study was similar to what is done in everyday clinical practice with patients in the initial years after the onset of schizophrenia. The study was not designed to cause relapse, but to observe patients for periods on medication and off medication, since this is what typically occurs in community practice. None of the patients who participated in the study were deliberately allowed to experience a relapse.

How was the study conducted? The study was conducted in three phases. Before entering each phase, the potential subjects were presented with both written and considerable oral information about the study. Oral information in the study constitutes 23 pages of summarized oral information that was provided to patients in addition to what was provided them in the consent forms.

Additional details were included at each subsequent stage of the process, and consent was obtained separately at each stage in the study. I won't give you the details in terms of time, in terms of some of the issues, in terms of specifics, but they are included in our information.

What is important is that patients receive medication at least every 2 weeks, and have their symptoms monitored by a psychiatrist. A case manager provided training in everyday living and coping skills and monitored symptoms. Patients and close family members were invited to a patient and family education program. Staff worked to keep family members informed about treatment unless patients exercised their right to restrict such information. Adult patients have the right to exclude family members from being involved in their care, if they wish, and some patients in this study exercised this right.

Following phase one, those patients whose medication had been monitored for at least a year and who were clinically stable were offered the opportunity to participate in phase two. Phase two was designed to mimic the common medical practice in the community, which is to give recent-onset schizophrenia patients trial periods off medication to determine if they can continue to do well without medication.

In phase two, study participants continued to be monitored but had a 12 week period on medication followed by a 12 week period on placebo, or vice versa. More frequent visits to the aftercare program were recommended as clinically indicated.

If the patients did not show significant symptoms during this period, they were offered the opportunity to try a longer period without medication to determine whether they would continue to do

well without continuous medication. During phase two, the researchers monitored the patient for any signs of exacerbation or research-defined relapse. In fact, in phase two, the researchers used more sensitive procedures than standard medical practice to determine at the earliest possible point if someone was experiencing a psychotic exacerbation.

Did the study intentionally cause subjects to relapse? No. Unfortunately, relapse among patients with schizophrenia is common, even with medication. None of the patients who participated in the UCLA study was deliberately allowed to relapse. As occurs in community practice, some of the study subjects did experience a significant increase in symptoms or relapse, but relapses are neither causable nor preventable.

It is in the nature of the disease itself that there is a relapse. Thus, in the UCLA study, patients off medication relapsed and patients on medication relapsed. In its review of the study, the OPRR report found no demonstrable basis for rejecting the UCLA IRB's determination that the methodologic design of the schizophrenic disorders research is scientifically and ethically justifiable. Indeed, they found that what was offered to the patients was appropriate clinical practice.

A crucial point that has often been overlooked is the clinical override aspect of this study. At any point in the study, the researchers could and, in fact, did override the study criteria to provide medication or other treatment if needed by the patient. The patient's best interests always came first.

Some patients in the UCLA study refused to go back on medication on recommendation. The physician cannot force adult patients to take or resume medication against their will without a court hearing in California.

The OPRR review found several areas of informed consent documentation that were insufficient and as a result we have made the necessary changes. It is important to note that over the 12 years of this project, there have been multiple changes in the informed consent documents. We believe that the informed consent process met the intent of providing fully informed consent to the subjects. The documentation in this case has been changed to meet the requests of the OPRR. I won't say anymore about that since that is well-covered in terms of our written comments.

As one result of the OPRR report, UCLA will add one or more subject representatives to its committee to review certain studies involving subjects with severe psychiatric disorders. We are currently seeking advice from a variety of sources, including patient advocacy groups, to assist us in identifying these representatives. These subject representatives will augment the three non-UCLA members already on the campus medical IRB.

UCLA shares OPRR's commitment to ensuring that people participating in research studies are properly informed about risks, and we are committed to minimizing those risks. We continue to welcome suggestions and recommendations as the understanding of the protection of human subjects in research continues to evolve. We are particularly mindful of the ethical issues surrounding the participation of subjects in psychiatric studies and the consequences of not participating in those studies.

It may now be time for the Nation to revisit the ethical guidelines articulated in 1982 by the President's commission for the study of ethical problems in medicine, biomedical and biobehavioral research.

Dr. ROCKWELL. The issues that we are addressing were attempted to be addressed in that report but obviously were not successful. UCLA is deeply committed to participating in the national discussion of these important issues.

Thank you.

Chairman WYDEN. Doctor, thank you. I will have some questions here in a little bit.

[Dr. Rockwell's statement may be found in the appendix.]

Chairman WYDEN. Dr. Fost, welcome.

TESTIMONY OF NORMAN FOST, M.D., PROFESSOR, DEPARTMENT OF PEDIATRICS, UNIVERSITY OF WISCONSIN MEDICAL SCHOOL

Dr. FOST. Thank you, Mr. Chairman and members of the staff. Thank you very much for the opportunity to speak today.

I am Professor of Pediatrics and director of the Program in Medical Ethics at the University of Wisconsin. I am past chairman of the American Academy of Pediatrics Committee on Bioethics. I am a practicing pediatrician and have been chairman of the IRB at Wisconsin for 17 years. I have done clinical research on the issue of informed consent and published articles on research in the emergency setting, one of which is attached to my written testimony. I have also been consulted by the FDA on this issue.

I would like to focus on the question of when, if ever, it is ethically or legally appropriate to administer experimental treatment, particularly in emergency settings, without the consent of the patient.

I would like to emphasize three points: One, there is confusion as to what is legally and ethically permitted under existing regulations; two, this confusion is not good for the rights and interests of present or future patients or for public confidence; and, three, it would be an error, in my view, to try to resolve this problem by insisting on inflexible standards of informed consent in all clinical trials.

Let me emphasize this point. The process of obtaining informed consent is a means, not an end. Its purpose is to try to figure out what the patient wants. Inflexible standards of consent can interfere with the goal of treating patients in the way they want to be treated. I will be returning to some practical suggestions about this.

Investigators and IRB's are caught between two sets of conflicting regulations. On the one hand, the FDA allows investigational treatments without the consent of the patient or his or her representative if, among other requirements, the patient is confronted by a life-threatening situation.

In contrast, the NIH regulations add a different restriction. Investigational treatment without consent cannot be of more than minimal risk, meaning that the probability and magnitude of harm or discomfort are not greater than those encountered in daily life

or during the performance of routine physical or psychological tests.

To make it more confusing, the FDA statutory language has different standards for drugs and devices.

This confusion results in inconsistency, paralysis and stretching of the term minimal risk beyond its intent. Let me be specific. As you have heard, there are new drugs that offer promise in preventing the devastating brain damage that commonly results from a stroke or head injury. Such patients typically cannot consent, and a relative is often unavailable in the narrow window of time when such treatment is likely to be effective, perhaps within hours of the time of injury.

In some hospitals, studies have been approved by an IRB and implemented without the consent of a patient or relative. In others, such studies have been prohibited. My own IRB has reviewed studies in which we believe waiver of consent is ethically and legally justified but have deferred approval because of a fear of sanctions from the Office of Protection from Research Risks.

The paralysis that results is not just a problem for the advancement of science and the interests of future patients or the interests of manufacturers, though it is a serious problem for those interests. It is a problem for present patients, many of whom who want experimental treatments, even though neither they nor their relatives would be able to consent.

This problem is sometimes simplistically framed as a tension between the interests of present patients on the one hand and science or knowledge or future patients on the other. That tension exists, but the interests and desires of present patients are also being sacrificed by the present rules. I would rephrase Dr. Katz's observation or question as to whether or not patients can be compelled to participate in such trials to a question of whether they can be allowed to participate in such trials.

In one large study involving experimental treatment in an emergency setting without consent from the patient or a relative, over 95 percent of the relatives later said they were appreciative that the treatment was begun. These are the relatives who are authorized under the rules to consent to experimental treatment. Had it not been possible to waive consent in that study, the result would have been a course of action opposite to what the relatives and presumably the patients would have wanted. This would have thwarted the purpose that consent is designed to achieve.

Mr. Chairman, I believe the central ethical point is this: Consent is a means, not an end. The end which it serves is the patient's interests, ideally as defined by that patient. We do not serve the interests of patients by insisting in all cases on informed consent from the patient. When next of kin are not available it is not always in the patient's interests or consistent with patient wishes to refrain from using that treatment just because a relative is unavailable. This is especially likely when an experimental treatment is the only real hope for treating a condition that has no standard treatment.

I, therefore, support some exceptions to the requirement for informed consent in emergency settings. Because of transgressions by

researchers in the past, I believe these exceptions must be drawn with great care.

I would like to close by offering some suggestions for additional safeguards, supplementing the existing protection offered by the multiple levels of peer review, IRB review, and review and exposure from publications. These suggestions are explained in more detail in the attached publication.

First, studies in which waiver of consent is considered essential should be reviewed by what I call a surrogate panel of patients and/or relatives. These are individuals who would not be actual subjects, but who are familiar with the disorder being studied. These panels or focus groups, if you will, have been very helpful in advising investigators and IRB's as to the likely wishes of actual patients and their representatives.

Second, studies in which consent is waived should be reviewed more frequently than others, including an assessment of the patient's or relative's response when they have been informed after the fact that experimental treatment has been started, what Dr. Caplan called debriefing. If objections appear, the IRB should be able to stop the study as early as possible.

Finally, the Director of NIH or the Secretary of Health and Human Services have the authority under present regulations to conduct an independent review of such proposals before they can begin. This review could be delegated to an Ethics Advisory Board or a national IRB such as Dr. Katz proposed, although I have some concerns about the delays on relying on such a process.

In summary, it is not in the interest of present or future patients to be excluded from promising investigational drugs and devices simply because they cannot consent when a relative is unavailable. Such an exclusion would violate the purpose of informed consent, which is to do what the patient would want, as best we can determine.

In my opinion, the inconsistency between the FDA and NIH regulations is urgently in need of repair. There are many patients with possibly treatable injuries who will die or become disabled without having the chance to benefit from promising therapies. For many, this is not in their interests as they would define them.

Thank you again for the opportunity to speak today.

Chairman WYDEN. Thank you, Dr. Fost. Those are very helpful suggestions and ideas that you have offered.

[Dr. Fost's statement may be found in the appendix.]

Chairman WYDEN. Dr. Briefel, why don't I start with you? I am not sure you were here for it, but Dr. Caplan essentially described the environment for those of you that are trying to work responsibly through these issues relating to institutional review boards, as a regulatory swamp.

As somebody who comes from the front lines in terms of dealing with these issues and trying to satisfy these multiple agendas, would you agree with Dr. Caplan's assessment that it is a regulatory swamp?

Dr. BRIEFEL. I wouldn't go that far, but I would say, as Dr. Fost pointed out, that we do have to reconcile different criteria for performing these studies.

One of the problems with the FDA regulations which allow treatment in life-threatening situations is that it would be very difficult to approve a randomized trial for one group that might be getting a placebo because, obviously, the placebo therapy wouldn't be expected to provide any improvement to the subject. So, that we try to limit our protocols to those which present minimal risks to the individuals if it can't be done in any other fashion.

So, it does make IRB's face typical problems in trying to get the protocols approved that they qualify for approval. So, it is difficult.

But I think the issue really comes down to whether or not—what is the ethical justification for approving studies without consent. That is what we deal with from a practical point of view.

Chairman WYDEN. What would be your counsel to Federal administrators in terms of how they might better guide local institutional review boards?

Dr. BRIEFEL. Well, I think some of the suggestions that Dr. Fost made were excellent. I think local IRB's, for the most part, can handle these problems if the criteria for approval which should be decided on a national basis are clarified.

For example, again, the minimal risk, what does that mean? That has really been an issue not just for these protocols but for many other protocols. It has been left up to individual IRB's. There is really some concern about how IRB's are interpreting these regulations, and perhaps a national debate about how they should be interpreted would be helpful.

Chairman WYDEN. I would be interested in your thoughts on institutional review boards that operate in foreign countries where it appears some of the research on new drugs and devices is conducted. What do we know about this area?

Dr. BRIEFEL. Well, if the studies are being done, for example, from Hopkins in a foreign country, they would also have to be reviewed by our own IRB. However, if you are just asking how IRB's differ in other countries from those in our country, they may either be nonexistent or I think in Europe they tend to be a little bit more lenient than what we do. So, ours tend to be stricter.

Chairman WYDEN. Well, we understand that you all are trying to be very sensitive to these matters, but what about commercial, freestanding IRB's? What are their relationships?

Dr. BRIEFEL. I really don't have very much information about those IRB's, so I would be hesitant to comment on those.

Chairman WYDEN. All right. Let's move on to you, Dr. Todd.

One of the concerns that the subcommittee has had is that drug companies may have misinterpreted some of the regulations regarding the issue of informed consent. In your response to the subcommittee's letter in January, you stated that the FDA exceptions found in 21 CFR, Part 50.23, permits you to proceed with your research. Now, this is something that we want to inquire about because it appears that the regulations look like they are meant to let someone use an experimental product because nothing else looks like it will work. But here, what you are talking about, it becomes a whole scientific study.

Now, did the Food and Drug Administration indicate to you that such an interpretation was acceptable or did you assume that you

were correct because the Food and Drug Administration didn't tell you otherwise?

Dr. TODD. We actually began our discussion of this product and its development with the Food and Drug Administration in 1990, when it became evident from early animal trials that we had an agent which might show promise in head-injured individuals. At that point, we began in-house discussions of how this procedure could proceed, how we could protect the autonomy of individuals and still bring this product to the largest group of people who would benefit from it as quickly as possible.

We have been in discussion with the FDA throughout this period of time. They have reviewed our protocols. They agree that it is applicable under that statute.

Chairman WYDEN. So the FDA did read your informed consent form?

Dr. TODD. They have. Yes, sir.

Chairman WYDEN. And did they offer any comments on it for any other emergency room research?

Dr. TODD. I am trying to think if they offered any comments. They probably did offer comments. I can't really remember what they were.

Chairman WYDEN. In order to avoid conflict of interest issues related to research contracts, you also have some comments we are interested in.

Part of your checks and balances makes use of payment scales in the timing of reimbursement to reduce bias. Based on Upjohn's experience, what do you consider the two or three most important safeguards you have instituted to protect the integrity of your data in emergency room research?

Dr. TODD. The emergency room research is really considerably different than that performed elsewhere in the hospital, primarily because of the timing involved and the need for the investigator to make a very quick, almost a split-second decision as to what needs to be done.

We have tried to avoid any additional conflict by things that you have mentioned such as the reimbursement schedule. Beyond that, we recognize that we need to educate the investigator that this is a partnership not only between the corporation and the investigator but also between the participating patient. That those individuals, even though unable to give their full, informed consent are partners with us in this research.

The investigators take that very much to mind and make their decisions based on those things which are in the best interests of the patient.

Chairman WYDEN. Have you all ever rejected an Institutional Review Board's suggested modifications for research that used exceptions to informed consent requirements?

Dr. TODD. We have. I don't know of any cases in the particular protocol that we are talking about. We have rejected suggestions which have been made to informed consents which we thought made them nonviable in terms of giving full information and disclosure. So, there have been times when we have rejected those, yes.

Chairman WYDEN. We would be interested in your elaborating on that for the record about those areas.

Dr. TODD. I would have to get back to you in writing if you actually want some examples, but there have been some situations. These primarily represent differences of viewpoint. As others have talked about, what is disclosure to one person may not be to another. But that has occurred.

Chairman WYDEN. We would like you to get back to us in writing with some examples. That would be helpful.

Dr. TODD. All right.

[The information may be found in the appendix.]

Chairman WYDEN. Now, Dr. Katz has advocated the possibility of a Federal centralized Institutional Review Board to address research that cannot use traditional informed consent methods. As a manufacturer, what kind of approach would you like to see?

Dr. TODD. At this point, we agree with, I think, the other panelists within this group that the institutional review boards, as they exist on a local level, if given proper guidance, are well-equipped to make decisions about not only routine protocols but those that require an exemption from the usual informed consent standards.

Now, we would propose that a wider national discussion of this issue be taken and that further guidance be provided to the institutional review boards on a local level.

Chairman WYDEN. Dr. Rockwell, let me move on to you.

The subcommittee reviewed the Federal findings and enforcement record. Is it correct that you all at UCLA are now on a 90-day continuing review program with the Federal Government rather than the usual 5-year review status which is the norm?

Dr. ROCKWELL. That is correct.

Chairman WYDEN. Now, they, as I understand it, have also directed UCLA to appoint a patient advocate as well. Why, in your view, is a patient advocate needed?

Dr. ROCKWELL. It speaks to the issue of the balance of the Institutional Review Board. At UCLA the medical school IRB consists of the 12 faculty members, four staff members and three community members, the balance is obviously on the behalf of the researcher, and I think the recommendation to have a potential subject or somebody representing the subject class, explicitly from that class, is an appropriate recommendation.

There are three community members of our medical Institutional Review Board who are there to represent the views of the community. This is simply to enhance that process, and we are in agreement with it.

Chairman WYDEN. I note that the Office for Protection from Research Risks as reported in the *New York Times*, said the researchers in the case that we have been talking about, altered the medical records of patients and then refused to give medical records to the patients or their families. That strikes me as an extremely serious matter.

Dr. ROCKWELL. It is indeed, if the allegations were, in fact, correct.

What, in fact, happened is that the research records were altered when additional data or information was available. There are some occasions when a particular nurse in the clinic used white-out which is inappropriate in a medical record.

There are no rules for how to correct data entries in a research record, although the current practice is to do the same thing that we do in a medical record, which is to strike it through, and date it, and initial it. But there were, in fact, some white-outs. The individual was counseled, and that happened as soon as it was identified.

Chairman WYDEN. In hindsight, what should have been done differently in the situation that Mr. Aller has been talking about? I mean, it seems to me as I have been listening to this that we had a number of people who were essentially high-functioning individuals who got sick in the trial. They seemed to feel strongly that they weren't clearly informed about the risk of getting sick. They were denied medication when they got sick.

Dr. ROCKWELL. That is not true.

Chairman WYDEN. Well, let me just complete this. This is what they have said. They have felt that this idea of the clinical override was not adequate protection.

What, if anything, do you think should have been done differently?

Dr. ROCKWELL. In retrospect, if there had been better guidance from, for example, from the Belmont report in terms of dealing with psychiatric outpatients, what particular additional protections needed to be built in. The Belmont report in its last chapter, basically, is not particularly helpful for that. That is one of our urgings, that we take another look at that process.

I think our Institutional Review Board and the multiple other agencies that reviewed these consent forms, demonstrates an evolving standard in terms of consent. What was adequate consent in 1972 or 1982 is not adequate in 1992 or 1994.

Chairman WYDEN. How did the institution react to the major findings of the Office of Protection from Research Risks? Maybe you could tell us how you changed your protocols or anything else in terms of how you have changed?

Dr. ROCKWELL. We responded to their recommendations and made the changes that they indicated that they thought were appropriate. The informed consent form was changed. What we had said previously is that the consent is a process. It is not a document. Nevertheless, we have now put into the document the items that they felt were missing. We have done the necessary things in terms of developing additional oversight on these projects.

Chairman WYDEN. Do you sense that this situation is likely to occur again? I mean, I think part of what is striking here is your view and the view of Mr. Aller seem to be about 180 degrees apart from each other. Is it your sense that there have been changes that have been sufficient to keep this kind of thing from happening again?

Dr. ROCKWELL. Well, I think we have the difficulty of doing research with a population that has some substantial risks. But the risks are both in terms of participating or not participating.

The risks also include taking the medication or not taking the medication. These are not innocuous medications. They have permanent side effects that happen in some of these patients. Their exposure to the malignant neuroleptic syndrome is there. These are medications that patients do not like to take. They are unpleasant.

They cause all sorts of what we call side effects, but they would call main effects.

So, it is important that this research be done. We want to reduce the number of patients exposed to medication inappropriately while identifying people who are at risk of relapses as quickly as possible to put them back on their medication.

Chairman WYDEN. Let's set aside the specific situation with Mr. Aller for a minute.

Why don't you, if you would, tell us how UCLA goes about dealing with informed consent issues in other sorts of clinical trials when we are talking about vulnerable people? And I think what would be helpful to me is how the University goes about setting up clinical trials differently with respect to the vulnerable individuals than they would with say an adult who had no such problems.

Dr. ROCKWELL. If you define vulnerable people as people——

Chairman WYDEN. Children, those with mental problems.

Dr. ROCKWELL. The requirement in terms of the Belmont perspective is institutionally, mentally disordered patients, what we are talking about in our projects and in most of the projects, who are outpatients, clearly are able to present themselves clearly and directly, as Mr. Aller was certainly able to do this morning.

The protection for vulnerable projects would be run through the Human Subjects Protection Committee, the Institutional Review Board, with the same kind of process that would happen with any other subject. There would be an attempt by the three non-UCLA members to take a harder look at those projects perhaps in terms of the vulnerability of the class. In the future I suspect that there would be a request or a demand that the subjects be represented on the committee in some way, and that is probably an appropriate request.

Chairman WYDEN. Let me make sure I understand something, because I may have got something that you didn't intend.

We are talking about these research subjects who are vulnerable at the time of trial. I am interested in knowing how they would be treated differently when they are vulnerable at the time of trial, rather than I guess as you compared Mr. Aller today, to someone who clearly was a normal adult. Now, I know that you are not saying that Mr. Aller should be analyzed on the basis of how he appeared today. But given the fact that the relevant time period is at the time of trial, what would be some of the key distinctions between how you would treat someone at the time of trial who was vulnerable and someone who was not?

Dr. ROCKWELL. The key issue there is in terms of the phased process of consent.

So, for example, in identifying a potential subject for the research, the researchers would get permission from the physician responsible for the patient, from the patient him or herself, in terms of having a diagnostic interview at the time when they were in the hospital or shortly after the time that they left the hospital. The first consent is, basically, a consent to have a diagnostic interview.

The diagnostic interview then would be carried out by a mental health professional who recognizes that informed consent is a major issue.

What would happen in terms of permission to get into phase one of the study, which is to come into the study on medication for a period of time and to be followed through that period of time, the subject would review the informed consent form, would have all of their questions answered.

They would be asked to repeat back to the person seeking the consent and to a witness their understanding of the study so that they would say, "this is a study in which I am going to be on medication. At some point, you may ask me to go off of medication. I may relapse in my symptoms if I do that, and I understand that I may relapse on medication."

So, the subject would be asked to produce back to the investigators their understanding of the process. Subjects who were not able to do that were not included in the process. So, that, basically, these were people making, in spite of the fact they may have psychiatric symptoms, reasonable decisions and decisions that could be described to them and explained to them and explained back by them to prove that they knew what they were getting into.

Chairman WYDEN. Now, you said that the informed consent process is an evolving one, that the rules are changing. What are some of the factors driving this evolution, as you see it, in informed consent?

Dr. ROCKWELL. Well, I think activities such as this gathering today are factors that move this process along.

I think if we go back and look at the history of informed consent we have seen progressive improvements in terms of informed consent. Certainly Professor Katz and others have made major contributions in terms of our understanding of what we are obliged to do, and I think we have, in fact, made major progress in terms of eliciting informed consent.

But it is a process. It is not a document. So, it has to take place over a period of time. It is a timely, lengthy procedure, particularly in very complex areas, and this happens to be one.

Chairman WYDEN. Now, is this the first time that patient representatives are going to be included on a UCLA medical Institutional Review Board?

Dr. ROCKWELL. This is the first time that specific patient subjects would be included, yes.

Chairman WYDEN. Let me move on, if I could, to you, Dr. Fost. You mentioned an ethics advisory board. Some have suggested that there ought to be a national board to review informed consent procedures. Maybe you could highlight some of the differences between these various ways in which boards might play a constructive role in this area.

Dr. FOST. Well, the originally termed ethics advisory board was created as an entity for the Secretary of Health and Human Services to review research involving fetuses and reproductive issues. It never quite got off the ground. But the concept, I think, could be applied to many of the issues that you are concerned about today.

I am very sympathetic to Dr. Katz's suggestion that there be some national entity but that its scope be narrow. I think we have to be careful about creating a much larger bureaucracy.

But, for example, studies of this sort we have talked about today in which consent would be waived. I think that is a sufficiently

problematic area that it might be appropriate to have an advisory board to the Secretary.

The Secretary presently has the authority to review such studies before they begin, and he or she might benefit from having an advisory board with representation from patient groups and so on. It could be called an ethics advisory board or something else.

Chairman WYDEN. What extra precautions do you think are appropriate where you are talking about children for research in these areas?

Dr. FOST. The ones that I mentioned. I agree with Dr. Caplan that we want to have an added level of scrutiny when we are dealing with children because they are vulnerable in other ways that even adults are not. But the ones that I mentioned I think would be desirable—surrogate parents. In fact, we have used this in a clinical trial——

Chairman WYDEN. Tell me what a surrogate parent is.

Dr. FOST. I have been a co-investigator on a very controversial trial on randomized treatment of cystic fibrosis in the newborn period, screening of newborns for that. Half of the patients would get early treatment and half would not. It is a very controversial study reviewed by NIH and many other levels.

Before we embarked on it, we convened several panels of parents of CF children, parents of normal children. These were people who would not be eligible for this study because their children were already past the newborn period. We asked them, how would you feel about this study? They were able to speak to us in a much more candid way than real subjects do because they are not quite so vulnerable. Time is not an issue. We got many helpful suggestions from them.

But the bottom line was we got 100 percent approval of going ahead with the study, with some changes that they suggested that we thought were desirable.

So, I call them surrogates because they are not legal surrogates but they can speak for parents of CF children in the sense that they know what it is like, they understand what the issues are, and they have got more time to reflect on it.

Chairman WYDEN. But these would be parents whose youngsters did not have the particular affliction, but your sense would be, as parents, they could better identify than someone who wasn't a parent?

Dr. FOST. We used both. We used parents who were—did have children with cystic fibrosis, which was the entity that we were studying, and we also used parents of normal children. But I would strongly recommend that the surrogate panels be people or relatives who are familiar with the affliction.

There is a counterpart in the prisoner regulations. Any time—by regulation, any time we do research on prisoners there has to be somebody there who knows something about prison life, who is an advocate for prisoners. I think it is a very good—it is a mini-surrogate panel. It is only one person. But I think it could be good.

Chairman WYDEN. Well, I think it is a really fascinating idea.

I was going to offer to volunteer because I have two youngsters, but they do not, fortunately, have the affliction you are talking

about. The point you are making is that you have to have somebody who really understands what it is like on a day-to-day basis.

Dr. FOST. Exactly.

Chairman WYDEN. You said it very well. Excellent panel.

In the interests of time, we are going to excuse you.

We are going to take a 10-minute break, and then we are going to have our final panel: Dr. Gary Ellis, Director, U.S. Department of Health, Office for Protection from Research Risks; and Mary Pendergast, Deputy Commissioner, U.S. Food and Drug Administration.

[Recess.]

Chairman WYDEN. Let us have the subcommittee come to order.

Let me advise all of you it is the practice of the subcommittee to swear all of the witnesses who come before the subcommittee.

Do any of you have any objection to being sworn as a witness?

Please rise and raise your right hand.

[Witnesses sworn.]

Chairman WYDEN. We are going to make your prepared statements a part of the hearing record in their entirety.

All of you have worked with this subcommittee on many occasions before. Let me first state that we very much appreciate the cooperation of all parties in this investigation, and it is very clear that this is a complicated field, and we have appreciated the way you all have worked with us.

If you could, in 5 to 7 minutes or so, perhaps highlight your major concerns, that would be helpful, and we will make your prepared remarks a part of the record.

Dr. Ellis, it has been some time since you have been before the subcommittee, but we welcome you. Please proceed.

TESTIMONY OF GARY ELLIS, DIRECTOR, OFFICE FOR PROTECTION FROM RESEARCH RISKS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, BETHESDA, MARYLAND, ACCOMPANIED BY F. WILLIAM DOMMEL, JR., SENIOR POLICY ADVISOR

Mr. ELLIS. Thank you very much, Mr. Chairman.

I am Gary Ellis, the Director of the Office for Protection from Research Risks—OPRR—and with me today is OPRR Senior Policy Advisor, Bill Dommel. We appreciate the opportunity to testify, but, moreover, we are glad you are having this hearing.

You may be aware that this is the ninth hearing related to the protection of human subjects in research since January 15th when Senator Kennedy and Mr. Markey began the year investigating research at the Fernald school in Massachusetts. With each successive hearing this spring, general awareness of and alertness to protecting human subjects has grown.

Although it is ironic for me to say in the wake of this morning's testimony, it is fair for me to say that human research subjects have never been more well-protected than they are at this moment.

OPRR implements regulations regarding the protection of human subjects, that is 45 CFR, Part 46, that have been promulgated to apply to the entire Department of Health and Human Services. In doing so, OPRR oversees a well-developed yet ever-evolving system of protection of human research subjects. My statement describes

the interests not just of NIH but of the Department as a whole in protecting human subjects in research, a responsibility of enormous weight.

Next Monday, May 30th, marks the 20th anniversary of the formal promulgation on May 30, 1974, of the Department's regulations for protection of human subjects in research. This enduring and vigorous system of protections is designed to preclude the very problems that we have gathered here today to discuss. Yet it goes without saying that we are always interested in improving the system.

This system of protecting human subjects is based on a succession or chain of judgments made by people in the context of Federal regulations. People like you and me look at research protocols and weigh risks and potential benefits.

There is no computer program for this. There is no generic formula. This isn't done wholesale. It is done retail. One size doesn't fit all. This is custom work.

Who is involved in protecting human subjects? The architecture of the current system involves at least half a dozen levels of protection.

First and foremost, there is the interaction between research volunteer and research investigator. This is where the informed consent process takes place. It must be an ongoing, dynamic process as new information becomes available or as new questions are posed by the research volunteer. The informed consent document is one component, the written component of the informed consent process.

The Institutional Review Board conducts prospective and continuing, ongoing review of research. This board is composed of a group of individuals with no formal interest in the research. Its review is a local review by individuals who are in the best position to know the resources of the institution, the capabilities and reputations of the investigators and the staff, and the prevailing values and ethics of the community and the likely population of research subjects.

In my statement I emphasize the multiple layers of protection inherent in the system. I know you are most concerned about the possibility that this system can somehow fail. What is the possibility of a catastrophic failure in human judgment running through six or more layers? I would characterize that possibility as slight.

You get a sense of the kinds of problems that occur and actions taken to address them from some recent actions taken by OPRR. In one instance we heard about this morning, OPRR was concerned whether there was a proper explanation of risks in the informed consent process for a study involving persons diagnosed with schizophrenia.

OPRR first rebuked the IRB for poor oversight of the informed consent process; second, directed that the informed consent process be revised; and, third, instituted very close monitoring of the institution's human subjects activities. That monitoring will continue for some time.

At a second institution, the concern was a misuse of an expedited review process by the IRB. OPRR identified a failure of leadership within this IRB, and the IRB chairman subsequently resigned.

At a third institution, the concern was whether or not the IRB was properly conducting the required continuing annual review of research. The institution was called upon to demonstrate its ongoing review process to OPRR.

We have heard this morning about vulnerable subjects. What populations are judged to be vulnerable? IRB's watch out especially for research involving children, prisoners, pregnant women, individuals with mental disabilities, individuals who are economically disadvantaged, and individuals who are educationally disadvantaged.

The HHS regulations provide extra protection for vulnerable subjects in several ways. If an IRB regularly reviews research that involves a vulnerable category of subjects, consideration must be given to including as IRB members one or more individuals who are knowledgeable about and experienced in working with the vulnerable subjects. When some or all of the subjects are likely to be vulnerable to coercion or to undue influence, IRB's must see that additional safeguards are included in the study protocol.

Specific, detailed protections are actually written in to HHS regulations pertaining to pregnant women, fetuses, human ova fertilized in vitro, prisoners and children.

All present today know how integral—how crucial—the process of informed consent is. Federal regulations specify eight required elements of informed consent.

HHS regulations provide an avenue for waiver of consent in certain narrow circumstances when, in the IRB's judgment, four specified circumstances pertain. IRB's are required to make and document these judgments.

The HHS regulations provide one additional avenue for waiver of consent. In very rare circumstances, the Secretary may waive the applicability of informed consent—or some or all of the other provisions of the regulations—to specific research activities or classes of research activities otherwise covered by the regulations.

OPRR believes that the provisions for waiving informed consent spelled out in the HHS regulations are workable. It should be clear, too, that the four regulatory criteria for waiving informed consent are quite restrictive. Waiver of informed consent is clearly not compatible, for example, with research involving greater than minimal risk to the subject.

Although the Department actively conducts and support biomedical and behavior research involving human subjects, HHS regulations describe certain ethical boundaries to that research. Is this position inimical to progress in certain especially risky areas of research?

Consider the viewpoint of our earlier witness, Jay Katz: "I value respect for the dignity and integrity of man," said Professor Katz in U.S. Senate testimony 21 years ago, "even more than the advancement of science. For progress is an optional goal, and we have much more to lose, as we have lost already, from the erosion of the moral values which inevitably follows any unauthorized invasion of man's mind and body."

OPRR shares with you, Mr. Chairman and members of the subcommittee and with Professor Katz, a commitment to protect the rights and welfare of our fellow citizens who elect to volunteer for

research studies and who, in doing so, ultimately improve the lot of us all.

Thank you, Mr. Chairman. We are pleased to answer any questions about our system for safeguarding the rights and welfare of human research subjects.

Chairman WYDEN. Dr. Ellis, thank you very much, and we will have some questions for you in a moment.

[Mr. Ellis' statement may be found in the appendix.]

Chairman WYDEN. Ms. Pendergast, we welcome you. You have always been very helpful in working with the subcommittee. Please proceed.

TESTIMONY OF MARY PENDERGAST, DEPUTY COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MARYLAND; ACCOMPANIED BY ROBERT TEMPLE, M.D., DIRECTOR, DRUG EVALUATIONS, AND SUSAN ALPERT, M.D., ACTING DIRECTOR, DEVICE EVALUATIONS

Ms. PENDERGAST. Thank you, Mr. Chairman.

I am Mary Pendergast, Deputy Commissioner of the Food and Drug Administration. With me today are Dr. Robert Temple, Director of the Office of Drug Regulation in FDA's Center for Drug Evaluation and Research; and Dr. Susan Alpert, Acting Director of the Office of Device Evaluation in FDA's Center for Devices and Radiological Health.

FDA regulates human research in support of marketing applications for drugs, biologics and medical devices under the Federal Food, Drug, and Cosmetic Act. We are pleased to be here today to discuss the Agency's policy with respect to obtaining informed consent, particularly in clinical trials where patients are unable to give consent because they are unconscious.

The issues involved are extremely important. Because the studies affected by this policy involve fatal diseases and conditions, usually with no adequate treatment, the patients are an extremely vulnerable population entitled to maximum protection.

Mr. Chairman, we share your view that all research must be done in an ethical manner. In the vast majority of FDA-regulated research, the ethical mandate requiring respect for the autonomy of patients is satisfied when the patient is able to give informed consent.

If a patient cannot consent because of age, loss of consciousness, or other mental incapacity, the investigator must obtain the consent of the patient's legally authorized representative.

Our main focus here today, though, is that exceedingly small subset of research where it is impossible to obtain the informed consent of either the patient or the patient's representative.

This situation arises only when four conditions are met: First, the patient is unconscious or otherwise mentally incapacitated; second, the patient's situation is life threatening and there is no alternative therapy that has an equal or greater likelihood of saving his or her life; third, the experimental intervention must be given almost immediately if it is going to have any chance of success; and, finally, there is no time to find the patient's representative and obtain informed consent from that representative.

The type of research that might fall into this category includes research involving patients who have had a cardiac arrest or traumatic brain injury.

Our overriding principle is that this research, if it is to be done at all, must be done ethically. The requirement covers many factors other than informed consent. For example, research that is not well designed and that cannot lead to definitive scientific answers about the tested drug or device is not ethical. No research should subject any patient to risk without the concomitant benefit of scientific knowledge.

Similarly, in all research, there is a requirement that accurate and full disclosure be given by the investigator to both the Institutional Review Board and any patient in the research program. The disclosure includes the program's purposes, foreseeable risks, alternative treatments, possible benefits, and all other relevant matters. In addition, once a study is initiated, the investigator has an obligation to adhere to the study protocol approved by the IRB.

Many of the abuses in research that we have identified in the past were failures to follow the rules regarding truthfulness and faithful adherence to the protocol, which is required of all research.

As I indicated, the essential core of FDA's informed consent regulations is that informed consent must be obtained from a patient or his or her representative. There is, however, an exception to this rule which derives from the device amendments to the Federal Food, Drug, and Cosmetic Act.

That law permits exceptions from the requirements in an emergency situation where, again, four conditions are met:

First, the patient must be confronted by a life-threatening situation necessitating the test article's use.

Second, informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally effective consent from, the patient.

Third, time is not sufficient to obtain consent from the patient's legal representative.

Finally, no alternative method of approved or generally recognized therapy provides an equal or greater likelihood of saving the patient's life.

The regulatory requirements for such an exception appear principally directed at individual uses of treatments. They do not apply as easily to clinical trials, especially to a randomized trial where one group gets a placebo instead of the test treatment. Nonetheless, the Agency has concluded that in some circumstances randomized trials can be conducted in emergency settings under the regulations permitting an exception to the informed consent requirement.

This is one area where we will be giving more explicit advice to institutional review boards and to the research community generally so that they can evaluate carefully and thoughtfully research that is proposed under the regulatory exception for informed consent. We are also considering modification to this part of our regulations in order to provide more clarity and guidance.

There are other reasons why we believe the regulations covering informed consent need to be revised and updated. One reason is the advances in technology that have the potential of bringing new

treatments for previously untreatable conditions such as cardiac arrest or strokes, when patients are unconscious and cannot give informed consent. We are very conscious of the need for rigorously designed studies on interventions in acutely life-threatening situations, and we do not wish to impede that research. Without such studies, new therapies for critically injured patients may never be validated or used.

Alternatively, such therapies could be widely used without any rigorous demonstration of their effectiveness through clinical trials.

Another reason for updating the regulations is the changing attitude toward the right of patients. When the FDA's regulations were first written, the desire was to protect vulnerable patients so that they would not be used as guinea pigs. Investigational products reviewed from the standpoint of their risks and a paternalistic attitude of protection prevailed.

In the 1990's, the emphasis on paternalism has been joined by an emphasis on the right of an individual to access promising new therapies. Yet at this time a public policy consensus has not emerged.

We believe it is important to define and seek some consensus on precisely how and in what circumstances patients who cannot consent can be enrolled ethically in such studies. To this end, we are reviewing our regulations and we are exploring with the National Institutes of Health ways in which we could obtain the broad public input bearing on this issue.

As we review our regulations and practices, we will also coordinate with any other Federal bodies that will be considering similar informed consent issues.

We intend to sponsor soon, with NIH, a workshop as a forum for interested patients, physicians, ethicists and members of institutional review boards to express their concerns and suggestions. We, as part of this workshop, hope to convene a group of experts who will be able to discuss the very complicated ethical issues raised by this type of research.

We recognize the rights and obligation to protect patients. Yet, at the same time, we would like to see new therapies for terminal diseases.

We are ready to answer any questions.

Chairman WYDEN. Thank you very much.

[Ms. Pendergast's statement may be found in the appendix.]

Chairman WYDEN. Let me say right at this point that I am somewhat perplexed, and I need to have you all clarify for me the status of what is going on.

Dr. Ellis, a good man who whom we have worked with on many occasions, says, by and large, everything is in pretty good shape. He says there are occasional problems, but, by and large, and to use his words, people have never had any more protection.

Ms. Pendergast, someone else who has worked with the subcommittee and also a very good person, I believe, is making an announcement today, that the FDA and the Government overall is, in effect, announcing a project to update informed consent regulation.

Am I missing something here or is that what is going on, Ms. Pendergast?

Ms. PENDERGAST. We, the FDA, along with Dr. Varmus, the head of the National Institutes of Health, have been listening to the concerns of the clinical investigator community and the institutional review boards when they tell us that they have some confusion and they would like better guidance.

At the same time, we know that people of good faith have very different points of view about when, if ever, this research could be conducted. So, we would like to broaden the opportunities for public input and discussion on these matters. Where that will go, I cannot say for certain, but we are presenting to you that we are open to taking a very hard look at this situation.

Chairman WYDEN. So the FDA, at this point, does not have a timetable for this particular effort but clearly is prepared to undertake a major reexamination of informed consent and do it in concert with Dr. Ellis's operation and others at the Federal level?

Ms. PENDERGAST. That is correct. I think, as you realize, there is a model of Federal policy that all agencies attempt to adhere to with respect to informed consent issues. No single agency is an independent actor here. I think that that is an important factor and one we should all recognize.

The FDA doesn't, can't and won't go off and do any action here unilaterally. But we do think it is time to broaden the debate.

Chairman WYDEN. Well, I think it is very appropriate that these policies be reexamined.

Let me move on then to what this reexamination would consist of. As you know, one of the things that has been particularly troubling has been the apparent inconsistency between the Food and Drug Administration, and the National Institutes of Health, with respect to experiments done without consent and when that is appropriate.

The Food and Drug Administration seems to say that the experiment must offer the best hope in a life-threatening emergency, and the Health Institute seems to say that the experiment must pose minimal risks. It has been described in the press as no more than what a routine doctor visit might involve.

Is, as part of this reexamination, one of the central objectives to try to come up with a common definition that could be employed by both the FDA and by the National Institutes of Health so that we might in effect, to use Dr. Caplan's phrase, drain this regulatory swamp and bring some clarity to this? Is one of the objectives of your reexamination to make consistent the standards here?

Ms. PENDERGAST. I think there is a qualified yes to that answer. Back in 1981 when the FDA's regulations were promulgated, the FDA thought it was—indeed everyone thought it was—promulgating regulations that were, in fact, consistent with the Office of Protection for Research Risks. The only differences were ones that were mandated by our statute. At that time, all attempts were made to make sure that the two regulations were, as far as was possible, consistent. Indeed, we have the same definition of minimal risk.

But the kind of research that we are looking at today was research that was not envisioned back then. So, I think that what we see here is that, while we thought we had consistent regulations, as you attempt to put them into practice in this exceedingly small

subset of cases, there are small fractures in the common wall of our regulations, and that is what we are willing to take a look at.

Chairman WYDEN. Well, I hope that as you go after this effort that this be one of the highest priorities because this is something that we have heard repeatedly from essentially all parties; that the Federal Government shows up, caucuses and then heads in opposite directions, with one agency going in one direction, and another agency going in the other.

So, I realize that this is a difficult task, to be sure. But I would make it a top priority of this reexamination effort, which I have to tell you I think is very welcome and will be well-received.

Ms. PENDERGAST. Thank you. May I make a point on that?

Chairman WYDEN. Please.

Ms. PENDERGAST. I think, with respect to the underlying philosophy or principles that are applied, OPRR and FDA are in lockstep. We both recognize that persons who cannot give informed consent are an exceedingly vulnerable population that deserves very broad protection. We also recognize that this kind of research can be done only in very limited circumstances after very searching inquiry.

Yes, while it is true the particular T's and I's that we all have to cross and dot are different with respect to OPRR regulations and the FDA regulations, the core values underlying those two sets of regulations are very similar.

Chairman WYDEN. Dr. Ellis, do you think you folks are in lockstep?

Mr. ELLIS. Well, I am always pleased to have an endorsement of the Department's regulations.

We are in step to the extent that the FDA believes, as OPRR does, that when you have an individual who is unable to give consent for whatever reason, then this is a fully autonomous individual worthy of respect for person, that although that individual is, perhaps temporarily, unable to express his or her wishes, he or she is still fully autonomous and deserving of respect.

That is why, in order for consent to be waived, there is a very high regulatory threshold. There are four conditions that must be met for a consent waiver under the HHS regulations. There are four different conditions in the FDA regulations to grant an exception—not a waiver but an exception.

We know that IRB's can handle these two sets of regulations, but where do we look for evidence of this?

Here is the periodical called IRB. It comes out every 2 months, and this is where thoughtful discourse occurs among IRB members around the country. This happens to be the current issue of IRB.

Within this issue, the IRB from the University of Nebraska is reporting its thoughts on a study involving incompetent subjects where it considered the issue of exception to informed consent under the FDA rule and waiver of informed consent under the HHS regulations. The IRB at the University of Nebraska writes: "This means that eight different conditions must be satisfied before such a study can go forward."

Eight different conditions. Well, that sounds onerous. I note there happen to be eight elements in informed consent in the regulations, so the number eight in and of itself is not a problem. We think that a requirement to meet eight conditions for undertaking

a study with an individual that cannot give consent is not onerous. There has to be a very narrow avenue to go down for this type of research.

Chairman WYDEN. Well, I hope that at the end of the reexamination there will be an effort to have harmonized to the greatest extent possible.

I have to tell you, Ms. Pendergast, when I read the two definitions that have been widely reported that—in effect to not have consent of the Food and Drug Administration, there has got to be the best hope for a life-threatening emergency, and then the Health Institute says that the experiment must pose minimal risks.

I say to myself that sure sounds like two different kinds of standards, but I guess what is really important is that this reexamination is a very useful step and we want to see you all come up with an approach that really does harmonize what the two agencies are doing. I think that will be of great value and will allow more research to be done in a fashion more consistent with the protection of the subject.

Mr. Ellis, one point of new business. Last week, we sent you a letter of inquiry with some material regarding treatment trials at the VA hospital in The Bronx. Is there anything you can tell us about that matter today?

Mr. ELLIS. We received information last week, essentially simultaneously from three sources, about research being conducted at the Bronx VA Hospital. We are initiating an inquiry into that to evaluate the compliance of this activity with Federal regulations. Our authority in this case comes from the fact that the Bronx VA Hospital has assured the Department of Health and Human Services, that it will comply with the HHS regulations for protection of human subjects. This written instrument was submitted by and through the Mount Sinai School of Medicine in this case, so The Bronx VA is assured through Mount Sinai.

We will use that written instrument as we do in every case where an institution has assured the Department of its intention to comply. We will use that formal written instrument and the human subject regulations to measure the performance of the institution, in this case, the Bronx VA. This is a time consuming activity. It is meticulous, and we will get right to it. We appreciate the referral by the subcommittee to us.

Chairman WYDEN. We have heard about a number of problems involving local institutional review boards, from Rhode Island, California, Minnesota and Maryland. Is there an inquiry under way with respect to these to ascertain if they are complying with Health and Human Services regulations?

Mr. ELLIS. If you would be so good as to list them again. Rhode Island Hospital, yes. Minnesota, yes.

Chairman WYDEN. California?

Mr. ELLIS. We do have an inquiry that I think you would consider relevant at the University of California, San Francisco. My guess is that is what you are referring to.

Chairman WYDEN. And Maryland?

Mr. ELLIS. I am unaware of an inquiry in Maryland. Perhaps that is something we can take up when you have more specifics and then I can respond.

Chairman WYDEN. With respect to foreign and commercial institutional review boards, we have had a number of leaders in the field express their concern to us about problems in this area.

Are these folks essentially unaccountable or in what way does the Government provide some measure of oversight over these organizations?

Mr. ELLIS. Let me respond in sequence. With respect to foreign institutional review boards, 24 different foreign nations received at least two grants in 1993 from the Department of Health and Human Services, to conduct human subject research. The four most prominent are the Netherlands, Sweden, United Kingdom, and Canada. We assure protection of human subjects at institutions in those countries just the same as we do domestic institutions.

With respect to what you have called commercial institutional review boards, we have never knowingly assured an institution that relies on a private, for-profit institutional review board.

Chairman WYDEN. Let me ask you about the UCLA study and the UCLA situation. Families in the instance we had of Mr. Aller testifying today felt that the Office of Protection from Research Risks essentially didn't go far enough. They also reported this to the *New York Times*, that they felt that there should have been a halt in the research and that it should have been condemned as "inappropriate human experimentation."

Essentially, they are making the argument that in effect, you had extremely vulnerable, sick individuals who in effect, under this, were going to have very serious relapses. What is your response to the families who said that the office didn't go far enough?

Mr. ELLIS. There is no question that this is very sensitive and difficult research with individuals that are vulnerable. In our assessment, we try to include expert consultation from individuals with no interest in this research, and we did that in the course of this investigation.

The best scientific advice that we were able to obtain indicates that this is a type of research that is doable, it is scientifically sound, and special protections need to be invoked. We faulted UCLA on the count of not accurately conveying all the risks of this research and not properly protecting the subjects.

Let me speak more broadly. Research on individuals with mental illness is something that is perhaps not adequately discussed and perhaps not adequately understood. Mental illnesses are just that, medical illnesses that may be of varying severity in different individuals and which might or might not impair an individual's capacity to consent to research.

Schizophrenia itself is a very heterogenous disease with highly variable outcomes. We must make room for the possibility that it is not feasible to distinguish the effects of schizophrenia itself from the effects of participating in this research. That is a possibility.

In any event, we directed UCLA to take serious actions to repair the situation in this particular protocol and we have also put them on what I would call a very short leash. We heard earlier of the ordinary 5-year license. The 5-year term of a multiple project assurance has been shortened by OPRR in UCLA's case to 90 days and that is renewable subject to our approval. That pertains to all human research at the University of California, Los Angeles.

Chairman WYDEN. Not long ago, the Food and Drug Administration shut down all research, albeit for a brief periods of time, at U.C. San Diego for a variety of reasons.

Has your agency done anything that sweeping?

Mr. ELLIS. The answer is yes. This is a good example of the cooperation between OPRR and the FDA. In the wake of an FDA audit, we receive an inspection report from the auditor. The individual who did the FDA audit at UCSD wrote in his notes that there was no evidence of continuing review of research more frequently than every 2 years.

That is not acceptable under the HHS regulations. The regulations require ongoing review of research at intervals appropriate to the degree of risk and, in any event, at least once a year. OPRR contacted the University of California at San Diego and said we have evidence from the FDA that you have not been conducting appropriate ongoing scrutiny of research; you have 30 days to demonstrate otherwise to us.

We went back and forth with UCSD, and they have provided us with a full digest of the more than 2,000 protocols at UCSD that involved human research subjects. They provided us the list 6 weeks ago. We have inspected it, and I would say that it appears that UCSD has indeed conducted proper, ongoing review of its research. In the course of that inquiry, as happens with almost every inquiry that we make, we find other—I will call them—odds and ends. I don't mean to trivialize them—they are items of interest to us at an institution. So, we will continue to work with UCSD, as with others.

Chairman WYDEN. Ms. Pendergast, Dr. Katz in the testimony he has given says that researchers in his view have a basic problem being honest and open to subjects, and that this problem can spill over into inadequate, incomplete, sometimes absent informed consent provisions. He also says that this is part of what he calls the dark shadow cast by the way physicians treat their patients during regular therapy.

I would be interested in the Agency's comments on this kind of assessment and whether there may be steps the Food and Drug Administration can take to provide better support for patients in essentially these two kinds of context, first research, but second, therapy as well?

Ms. PENDERGAST. I believe Dr. Katz is referring to the question of who decides what is best for the patient, the doctor, the patient, or the two of them working co-jointly. Over time, our society has shifted from a belief that doctors know best about what the patient needs to an understanding that patients should be fully advised of the kind of treatment, treatment alternatives and then the patient decides what kind of treatment the patient wants, whether that is in a normal therapeutic context or in the research context.

Now, we do not control medical practice. We do, however, control research, and there we think it is very important for physicians or clinical investigators to be crystal clear that what they are doing is research and that what they are doing, when they are doing research, is not necessarily in the best interest of any individual person who is a subject in that research protocol.

That impacts how we ask that clinical investigator to view every aspect of what he or she is doing. It influences the amount of disclosure they need to give to the IRB and to the patient, the carefulness with which a protocol needs to be designed, and the rigor with which they need to collect the data, because we believe it is important that the tendency is to segue from the view that you are not doing research, you are really helping the patient, and because you are really helping the patient and you are a physician what is best.

We try hard to pull on the reins so researchers don't segue from one point of view to another and make sure that they understand very carefully what precisely they are doing. That impacts how we write our regulations as well as how we inspect both institutional review boards and physicians.

Chairman WYDEN. You all have oversight responsibilities over institutional review boards, do you not?

Ms. PENDERGAST. Yes, we do.

Chairman WYDEN. Dr. Katz is one who thinks there needs to be better Federal oversight of institutional review boards. Do you generally agree with that?

Ms. PENDERGAST. We believe that some of the concerns Dr. Katz has raised with respect to patient selection and other matters are issues that are addressed in our regulations. I think that here we have a very difficult question as to the balance between intrusive Federal regulation and autonomous decisionmaking by IRB's. It is a very, very tough question and one which I think we are going to be taking a look at as we again review our regulations.

Research is infinite in its variety and there is no way that we could prospectively state what the IRB should think about any of the situations that the IRB will be confronted with.

Chairman WYDEN. Do you think it is appropriate that there be a sort of safety threshold that would apply to all subjects, federally mandated safety net?

Ms. PENDERGAST. Yes. I think that there is a safety threshold that is applied in that in any research, the investigator and the sponsor and the IRB all have to ascertain that the risks of the research are far outweighed by the benefits of the research.

Safety is a relative matter. You are willing to endure more if you have AIDS than if you have a headache. So, safety is relative, and here I think that the concept where the benefits have to outweigh the risks handles that.

Chairman WYDEN. What about the seriousness of conflicts of interest. You get the sense, having sat here for 4 hours, that virtually everybody in the field feels there are some really serious conflicts of interest out there. What is your sense, and what if anything is the agency looking at doing about it?

Ms. PENDERGAST. Conflicts are a difficult question. The rules governing IRB's already state that no one on an IRB can have any conflict with any of the research that is being considered by that IRB. So, no one can be in a position of passing judgment on whether his or her own research or that of a family member can go forward.

The kind of conflict you seem to be addressing today, though, is a more systemic concern about, can anyone affiliated with an insti-

tution turn down research if that institution will benefit? That is a very difficult question, but we haven't found a better solution. IRB's still provide the bulwark of protection for human subjects. We think they still play an important role.

Chairman WYDEN. Do we have a sufficiently strong system today to deal with flagrant kinds of abuses where there are conflicts of interest? It seems to me the example you gave is one that is sort of a gray area kind of matter. You have to look at the situation in a typical town where somebody serves on an institutional review board and somebody also is at the hospital.

But what I heard today sounds like pretty flagrant kinds of conflicts of interest that didn't seem to me to be getting picked up by the system. I am interested in whether you think that today we are at least getting at the flagrant conflicts, and what if anything, as part of your reexamination effort, is the agency looking at with respect to conflicts?

Ms. PENDERGAST. There are conflicts on several different parties' parts that we need to take a look at. The first is conflicts of the institutional review board members. Those, I think, are fairly explicitly covered by the regulations, which prohibit such conflicts.

A second order of conflict is whether the clinical investigator has some economic interest in the test article such that it might, to use Dr. Katz' words, sort of potentially, subconsciously bias that clinical investigator's work. That is the area of conflict that the FDA is already working on.

Principally, though, from the focus of data integrity, we want to make certain that when a sponsor submits a marketing application to the FDA, that we know of any potential conflict of interest that might be had by any clinical investigator who did the research.

So, we have been working on this issue, we have convened our science advisory board to discuss these matters, and we are hoping to address squarely the question of disclosure of any conflict of interest. As we have thought about it in the past, that is disclosure to the FDA. I think we need to look at the question of whether there should be similar disclosure to the IRB.

Chairman WYDEN. Please keep us up on the conflicts issue in particular. As you know, this is something we have been interested in for a number of years. It would be helpful to get apprised of that.

Ms. PENDERGAST. We would be pleased to do so.

Chairman WYDEN. We also heard from Dr. Katz about the matter of freestanding institutional review boards. He, for all practical purposes, is saying these profit-making entities are institutional review boards for hire in the sense that they are prone to make decisions based on their business interests rather than to protect subjects.

How serious a problem does FDA think this is, and what if any effort is being directed in this area as part of the reexamination?

Ms. PENDERGAST. We think this is a valid concern. But you should know that these entities are fully regulated by the FDA. They are obligated to conform to all of the Agency's institutional review board regulations. We inspect them and, as we have inspected them, we have found that they do not as a class have more difficulties than regular institution-based IRB's. That is not to say

they are perfect; they are not. But as a class, they are no better or worse than institution-based IRB's.

I think one of the things we have to keep in mind is they do serve an important function. There is a significant amount of research being done in this country that is office based. Doctors do the research in their offices unconnected to any hospital or other institution. If these freestanding IRB's didn't exist, there might be no IRB review of this office research, which we would also have great difficulty with. So, we understand why they are there, we inspect them and we keep a careful watch.

Chairman WYDEN. This also is something I have not heard before. Dr. Ellis, are you inspecting the freestanding commercial institutional review boards?

Mr. ELLIS. OPRR has never knowingly assured an institution to use this type of board, meaning a private, for-profit institutional review board. To the best of our knowledge, all the institutional assurances that we have issued have involved other than a private, for-profit institutional review board. This is something that is most germane to FDA.

Chairman WYDEN. We have also had some discussions with your staff, Ms. Pendergast, about institutional review board shopping, trying to find one that might be most favorable to a particular sort of research. Can you tell us what FDA has found in this area and what if anything the agency is doing about it?

Ms. PENDERGAST. IRB shopping obviously refers to when a clinical investigator goes to the institution where the clinical investigator thinks he or she might get approval. This has both good and bad connotations. IRB's are supposed to be autonomous entities that give their best judgment as to whether research could properly go forward at that institution. So, sometimes you have an IRB in an institution that is large enough, that the staff is trained enough, that they have the backup medical facilities such that the research could safely go forward; whereas another IRB may come to the conclusion that they are a small hospital, they don't have well-trained backup staff, and that research there would be inappropriate and they might say no. So, that is the kind of discrimination in decisionmaking that we expect of the IRB's.

The bad side of that autonomy is that there are some IRB's that are perhaps more lax than others in their assessment of the factors that need to go into patient protection, into a careful scrutiny of the research protocol. There the best way we have thought of to solve that problem is to work with the IRB's to train our IRB's, which we do with OPRR, to inspect them—we average an inspection of an IRB every day of the year—to give them guidance, and if they continue to fail in their responsibilities, we take regulatory action against IRB's, including suspension and disbarment.

Chairman WYDEN. My colleague from Texas, Mr. Combest, and also Mr. Koepsell, the president of Cardiologic Systems, have made a very valid point about how long it takes these small businesses, responsible, diligent small businesses to make their way through the FDA approval process.

Now, no one wants to see the system gamed by the bad apples. At the same time, there has to be a way for the many reputable,

honorable small businesses to get their devices and products to market efficiently.

I might add that when we heard from Mr. Koepsell today, he made no bones about saying protection of patients had to come first. He wanted to make sure that his products got a fair shake in marketing, in fact, and he said he only had a year really to hang on, but that his first commitment was to ensure that he met the standards in terms of human subjects.

What is going to be done as part of this reexamination to make it possible to Mr. Koepsell and many small companies we have in the Pacific Northwest and others across the country, that the Government is doing more to make the responsible small device company an entity that can get through the system and get through it in a way that will allow them to keep their doors open?

Ms. PENDERGAST. We think that we have a system that if it is used, and neither gamed nor avoided by companies, can help a company get a medical device to the market efficiently. What that requires is that before the company begins its first clinical trials, it comes to the FDA with its protocol and discusses that protocol with the FDA so that the company can learn from the FDA the types of studies that would be needed for approval, and so that the company can understand how to most efficiently do those studies with the fewest number of subjects possible, and so that the company engages in no false starts. That way, when the company finally does the studies and they submit a marketing application to the FDA, the data for approval is in that application.

That is our system and we constantly strive to make it better. I think the hiring Dr. Alpert to head this part of the Office of Device Evaluation is a good step forward. We recognize our obligation that if we are telling companies to come to the FDA, that when they come to the FDA, they get good, solid scientific and medical advice as to their design and that they get that advice quickly. We are working to improve the qualifications of our staff, we are trying to staff up, and are doing what we can in this area consistent with our other responsibilities and our resources.

Chairman WYDEN. Take the Ambu cardio pump kind of situation as an example. It seems to me what you are saying makes a great deal of sense, that you want to get it right so that folks don't have to reinvent the wheel later on as a result of a questionable science or something like that.

I understand that Ambu cardio pump had been given permission to do something like five trials before, in effect, anybody said hold on, you have got to go out and get an NVA; and that here was an example where, in effect, it wasn't done right the first time. You correct me if this is incorrect, but I am certainly interested in the objective that Ms. Pendergast is talking about, and I am wondering if Ambu cardio is an example where that wasn't carried out.

Dr. ALPERT. I think the issue with the Ambu cardio pump is as you stated it Mr. Chairman. There were in fact, investigations of this particular device that were going on around the country. They had been initiated without an investigational device exemption, an IDE, and done under an FDA-approved protocol, as Ms. Pendergast described, to ensure that the research program would in fact, expose the least number of patients, but a sufficient number to gath-

er the appropriate data to support a marketing application for that particular device.

The action that was taken by the FDA in asking those studies to be stopped was an issue of the lack of an FDA-approved investigational device exemption. This FDA process is one we feel is very important. We have something to offer in dealing with the companies very early on. We work with them in designing their research protocols, and identify the areas where we have concerns about the way the data will be gathered and then submitted to us to save repeated rounds of interaction when a submission for marketing does come in.

Chairman WYDEN. But if the system were working as it should, shouldn't someone have gotten that exemption early on rather than in a situation where IRB's cleared five trials and then later somebody should have had an exemption?

Dr. ALPERT. That is true. In the device regulations, there is a difference between what goes on with different types of devices prior to their marketing in terms of who is involved in determining the types and nature of the studies and locations of those studies. It differs from the way investigational drugs are regulated.

In device regulations, devices that are considered nonsignificant risk do not require a formal IDE with approval from the Office of Device Evaluation. Instead, the IDE responsibility essentially rests with the institutional review board. The investigators may go to the individual investigational review board and get permission to initiate that research. That is what happened in the case of Ambu. Each study was done individually with each IRB as a nonsignificant risk study.

Chairman WYDEN. Because I would hope as part of this reexamination effort—this would be for both of you—that greater effort be made in terms of ways to get these IRB's up to speed, because it seems to me that the Ambu cardio case, at the very least, was a situation where it seems some of these IRB's were not up to speed, having to get cleared all over. Maybe they should have had an exemption, maybe there should have been something else, but it still seems we are playing catch-up ball rather than do what Ms. Pendergast says, which is get it done right.

I would hope that as part of this reexamination effort, a special priority would be made to try to get institutional review boards up to speed early on so we get it done right once and maybe the Mr. Koepsells of the world and the like will find that that is something of real value to them because they can know with some certainty what the ground rules are.

I have a special interest in this because we are interested in trying to promote research in a wide variety of areas where people know ahead of time what is expected of them in terms of research trials. Because we think that will be of value in terms of getting them to put investment dollars into important areas in terms of drugs and devices.

The only other thing I had for you, Ms. Pendergast, is what is the status of the conflict of interest guidelines with respect to IRB's and research? Are they at Health and Human Services or where are they at this point?

Ms. PENDERGAST. The regulations that I believe you are talking about don't pertain to IRB's but do pertain to the disclosure of potential conflicts that clinical investigators might have. It would be a requirement for the sponsor to tell the FDA about it, not to tell the IRB. Yes, we are proceeding apace to get the necessary clearances for those regulations. This is another area where we can't act as single actors. We have to and want to coordinate our activities with those other parts of the Department that have similar situations; but everything is proceeding apace. We are very pleased.

Chairman WYDEN. When do you think it might get out of the regulatory system so that it will be the law of the land?

Ms. PENDERGAST. I am hopeful it will happen soon.

Chairman WYDEN. A month, 2 months, or 3 months?

Ms. PENDERGAST. I think in that ball park.

Chairman WYDEN. I appreciate your clarifying because I was not as precise as I should have been in the question. We want to see those rules with respect to conflicts get out, and if those can get out in the next couple of months, that would be helpful.

Certainly we would like to see as part of the reexamination effort that you are making that the agency look at this issue of conflicts at IRB's as well, because I think that is an important issue that we have heard a lot about today.

Let me recognize minority staff for any questions?

Mr. LEHMAN. I appreciate the Chairman recognizing me for questions. Is it correct to say that the Belmont report was issued 16 years ago that affected some of these issues we are discussing today?

Mr. ELLIS. That is correct. It was issued in 1978.

Mr. LEHMAN. Has there been harmonization or any changes in the regulations since then in these issues we discussed today?

Mr. ELLIS. The regulations for protecting human subjects were most recently put out for public comment, revised and issued in the summer of 1991, so not quite 3 years ago.

Mr. LEHMAN. Thank you.

Chairman WYDEN. You have been very helpful, and a 5-hour hearing ought to be enough for just about anybody. But I think all of you could hear that a lot of our witnesses, particularly on the first two panels, feel that all of us in Washington, DC have to do better. We look forward to pursuing these issues with you in the days ahead.

The subcommittee is adjourned.

[Whereupon, at 2:45 p.m., the subcommittee was adjourned, subject to the call of the chair.]

APPENDIX

STATEMENT BY

REPRESENTATIVE RONALD K. MACHTLEY

MAY 23, 1994

I am here today because I have learned that this subcommittee has singled out Rhode Island Hospital in Providence, RI., in a report prepared for the chairman, and has invited a witness to testify alleged abuses in its emergency department.

Rhode Island Hospital is the state's largest hospital. A non-profit institution, it serves as a major teaching hospital for the Brown University School Medicine. It has earned its reputation for excellence over a long and productive 130-year history

The hospital operates the state's only trauma center and, as such, provides emergency medical services to over 100,000 people per year. This averages 270 patients each and every day.

The hospital also recently opened a new Children's Hospital and serves as a regional referral center for pediatric care.

Rhode Island Hospital's charitable mission embraces service to all patients without regard to anyone's ability to pay for services. Rhode Island Hospital provides 22 percent of

all hospital care in Rhode Island, but provides nearly 39 percent of all uncompensated care delivered in Rhode Island.

Last year alone, Rhode Island Hospital provided over $28 million in care to individuals who could not pay for medical services they received.

In addition to its direct medical care provision, such as its HIV Clinic, the Hospital provides a wide variety of specialized services to the community.

Examples include: a career guidance and employment program, the regional poison center, a Child Development Center specializing in long term follow-up in birth defects, free immunizations for preschool children, health clinics at senior centers, scoliosis screening in public schools and extensive blood and bone marrow donor programs.

I, along with Rhode Island Hospital believe that compassionate care and patient interest must be a priority.

I know Rhode Island Hospital to be a superb institution, whose mission is to improve the health of people in Southern New England. I would ask this subcommittee and the public to bear in mind this excellent reputation as it considers the information provided today.

TESTIMONY OF

GREGORY ALLER

Former Patient of the
U.C.L.A. Aftercare Clinic
Los Angeles, California

BEFORE THE

Subcommittee on Regulation, Business
Opportunities and Technology

May 23, 1994

1301 Brockton Avenue #9
Los Angeles, CA 90025
(310) 479-5058

TESTIMONY OF GREGORY ALLER
May 23, 1994

Mr. Chairman and Honorable Members of the Subcommittee:

My name is Gregory Aller. I am a junior at U.C.L.A. majoring in political science.

I come today ~~ato~~ to describe my own experience in a schizophrenia research experiment at U.C.L.A. In addition, three families from the UCLA program asked me to speak on their behalf.

Back in 1987 I was diagnosed with schizophrenia. After being referred as a patient to ~~teh~~ the U.C.L.A. Aftercare Clinic for treatment, I had the experience of becoming not a patient, but a subject in high risk research. Though I signed a consent form, it turned out to be deceptive because it omitted what the research was really all about. The National Institutes of Health Office for Protection From Research Risks ruled on May 11, 1994, that the consent forms were not legally valid under Federal regulations because U.C.L.A. omitted foreseeable risks and alternative treatments. Over one hundred persons participated in this ressearch from 1979 to 1994, nearly fifteen years.

~~The~~ consent forms ^ I signed did not indicate the real purpose of the research ^ which was to study the relapse of patients. ~~In fact,~~

~~The~~ researchers ^ had published a scientific paper in the Journal of Abnormal Psychology (attached), claiming that the study was an improvement over previous retrospective studies, because this study was a prospective design that ensured ~~patietns~~ patients had severe or extremely severe relapses. Independent psychiatrists, psychologists, and bioethicists, confirmed our finding. We never knew any of these facts until much later.

The U.C.L.A. researchers first put everyone on one medication and one standard dose, adhering to a strict scientific protocol. The type of antipsychotic medication ^ used was "Prolixin." The researchers did not follow the drug manufacturer's instructions that medication should be adjusted to the individual needs of the patient and they did not tell patients that ~~they~~ they were in an experiment where the patient's welfare was secondary to the research goals.

In this first phase of the experiment I was lucky. Though some patients had a poor response to the standard dose, the standarized dose practically eliminated all of my delusions and made it possible for me to think relatively clearly. Since I had been diagnosed with paranoid schizophrenia, relief from the symptoms greatly improved my life. My family and I were ecstatic. I enrolled at Santa Monica College and during the next year I

earned a 3.8 G.P.A., got on the Dean's List, and worked fifteen hours a week. I was proud of what I was accomplishing. It was certainly the best year of my adult life. But what would follow became the very worst year of my life.

The doctors asked me to go off medication to prevent the onset of a potentially irreversible movement disorder called "Tardive dyskinesia." In mid 1989, Dr. Nuechterlein, the Principal Investigator, met with my parents and I and promised my parents that if I had a return of symptoms the medication would be reinstated. Dr. Nuechterlein said that since my parents knew me best, when they reported symptoms, I would get my medication back. My mother asked Dr. Nuechterlein about this matter several times, stating that our family did not want to see a return of symptoms, especially since I was doing so well and was close to realizing my dream of transferring to U.C.L.A. We trusted the doctors and I agreed to go off medication. What we didn't know was that the researchers had another agenda. As my parents would later discover in the protocols, grant applications and summary reports, the researchers had claimed that they were studying exacerbation and relapse that results from standarized doses of medication and withdrawal of medication. This is not what they told patients and their families.

During this second phase of the experiment, my symptoms gradually returned, but this was the research plan for all patients withdrawn from medication. However, this time my symptoms were much more severe than the symptoms at the onset of my schizophrenia. What ensued was a nightmare.

My ability to concentrate fell apart. I was unable to do school work.

I became manic and hyperactive.

Some days I would hardly sleep at all.

One night I woke up screaming, actually believing that I was sprouting another leg.

I started to have ~~apranoid~~ paranoid delusions about government agents chasing me.

I became violent with my father and threatened to kill him.

I believed there were hidden cameras on the wall of my parents' living room.

Much later, still in a delusional state, I started hitchhiking to Washington to assassinate President Bush.

Though I had slipped back into paranoid symptoms, my doctor asked me if I felt I needed medication. Since I was paranoid by that time, I said I was fine, I didn't need medication. ~~The doctor~~ Dr. Gitlin never delved into what was really going on in my life.

At one point during my psychotic relapse, I thought that the devil had entered our ~~house~~ apartment and had taken possession of my mother by entering her body. I thought this was horrible for her, but I believed I could scare or cut the devil out of her. I grabbed a butcher knife in the kitchen and called to my mother. Before I could reach her she fled into the bedroom and barricaded the door. My father was able to talk to me so that I put down the knife. I was willing because I thought that I had scared the devil out of my mother. Looking back, it's horrifying to consider what might have happened if my father had not been present.

Throughout my deterioration and disintegration, from late 1989 to May, 1990, my father called the project's staff, telling them that he thought I needed medication. Both my mother and father met with Dr. Nuechterlein in January, 1990, and he said that my symptoms might be fluctuating and temporary and the staff would watch me carefully. Dr. Nuechterlein persuaded my parents to wait. My father persisted in his angry phone calls, but the researchers said that they did not agree with my parents' assessment. I suffered from months of psychotic experiences.

Finally, on May 15, 1990, my parents persuaded me to go back on medication. The same day my father took me to UCLA and I received an injection of prolixin.

But over the next six months I didn't return to my former level of functioning. My parents felt it was necessary to see the Vice Chancellor of Research, Albert Barber, to explain what happened and to ensure that these kinds of events didn't happen to other patients and families.

On February 20. 1991, ~~they~~ my parents met with Vice Chancellor Barber and other administrators. ~~My parents~~ They told the U.C.L.A. staff that they believed that a murder or suicide could likely occur under the conditions we had experienced. I believe that my parents' warning was not taken seriously.

At approximately the same time, in late February or early March, 1991, the researchers withdrew medication from Antonio Lamadrid, another patient, a former UCLA student. After five years of treatment the researchers expelled him from the program. When Tony was withdrawn from medication, he repeatedly told his U.C.L.A. caseworker that he planned to commit suicide. But the U.C.L.A. researchers never even bothered to inform the Lamadrid family of of Tony's suicide threats.

Barely five weeks after my parents had warned the Vice Chancellor, on the morning of March 28, 1991, Tony walked up to the roof of U.C.L.A.'s nine-story Boelter Hall, and jumped to his death, fulfilling his plan to commit suicide. The police report on Tony's suicide stated that the Aftercare Clinic refused to permit the police investigator to talk to a witness and former patient from the Aftercare Clinic who had been staying with Tony prior to his suicide.

Later, I learned from the Lamadrid family that a phone call to Tony's aunt or to any of Tony's three brothers, two of whom lived within minutes of Tony, would have alerted the family instantly and they would have been there to help Tony. But the family never understood precisely what was happening until it was too late. Even after Tony's suicide, ~~Tony's psychiatrist~~ Tony's psychiatrist for the last five years Michael Gitlin, never spoke to the Lamadrid family to offer a simple personal condolence.

O.P.R.R. investigated the suicide and communicated with the U.C.L.A. doctors, administrators, and lawyers during the three year investigation. But O.P.R.R. never interviewed the Lamadrid family. O.P.R.R. reached its conclusions after reviewing evidence presented only by U.C.L.A. Let me describe what happened to other subjects in this project.

Gabrielle Guardino, nicknamed Gabby, suffered an excrutiating reaction to the standard dose of Prolixin, yet her doctors would not break the protocol and switch her to another medication.

Gabby's mother told me that the medication caused Gabby to vomit frequently, bite her tongue and the insides of her mouth until she bled, and Prolixin caused her to have the sensation of her skin crawling. Although aware of Gabby's suffering the doctors never told Gabby's mother, Sydelle, about the alternative medications.

What they did tell her was that Gabby had to stay on the medication or she would have to leave the program.

Finally, after eight months, Gabby couldn't stand the effects of the medication anymore and she quit the program. A lot of terrible things happened to her. She was raped by two men when she was psychotic. She served time in jail. Finally, an organization called "Children of the Night" found Gabby living in a park.

Gabby's mother wrote a strong letter of ~~coplaint~~ complaint to U.C.L.A.

back in 1985, carefully sending copies of her letter to U.C.L.A.'s key psychiatric administrators, including Albert Barber, Vice Chancellor of Research. U.C.L.A. never wrote back to Sydelle Guardino.

As a patient, I find such research outside the boundaries of human decency. I ask you, who would ever want to be kept in the dark about another dozen medications that might have helped.

Let me describe one more UCLA case.

Frank De Balogh Ph.D. asked me to speak on behalf of his younger sister, Elizabeth. Elizabeth was living successfully at home.

Then, as Frank De Balogh explained to me, the U.C.L.A. researchers decided to withdraw medication from Elizabeth.

Elizabeth suffered an extremely severe relapse. No informed consent had been obtained and the foreseeable risks from severe relapse had not been described at all to the family.

I quote from the report submitted to O.P.R.R. by Frank De Balogh:

"One Saturday morning in May, 1985, I received an urgent call from my mother who requested my help ~~crying~~ saying that she could not handle Elizabeth. I found Elizabeth not speaking; not eating, not sleeping, pacing about, pushing her mother away, turning lights on and off, opening and shutting doors and windows. In short, she was acting psychotic. When I called the U.C.L.A. phone number for help, all we got was a message that they would be

available during normal business hours Monday through Friday and that they could not be reached on the weekend."

Dr. De Balogh states that U.C.L.A. had not provided emergency instructions or plans in the event of a relapse. Since immediate care was necessary, Dr. De Balogh checked Elizabeth into the Los Angeles County - U.S.C. Hospital, and Elizabeth has remained institutionalized since that episode in 1985.

Dr. De Balogh describes Elizabeth's current condition:

Due to a fear of cars and freeways Elizabeth is unwilling to visit any of her family member's homes.

She is afraid to see her cousin, whom she considers to be a "witch."

She has continuous suspicions about ~~chr~~ her food being poisoned.

She doesn't ~~wtch~~ watch television in her room because she claims that she watches "television" in her mind.

In short, Elizabeth remains gravely disabled, most probably permanently institutionalized and under conservatorship.

In addition to the failure to obtain valid informed consent, Dr. De Balogh highlights the lack of administrative oversight by the U.C.L.A. Neuropsychiatric Institute and the lack of medical emergency planning required for such high risk research.

Would I have ever signed the U.C.L.A. consents if I had been provided with full disclosure and I had known the real purpose of this study? Absolutely not. And I don't think anyone else would have, either.

I don't believe that this research could have taken place with proper disclosure and informed consent.

I believe that the researchers viewed people with schizophrenia as subhuman. I doubt whether any doctor who works at the U.C.L.A. Medical Center would ever allow a son or daughter to become a subject in this experiment. In fact, after I obtained a few of my patient records, O.P.R.R. confirmed that my psychiatrist's initials appeared next to white-outs, obliterations, and alterations in my records.

Unfortunately, the end is not in sight. U.C.L.A. has experimented on hundreds of veterans with schizophrenia, without indicating foreseeable risks and alternative treatments in the informed consent forms. The Office For Protection From Research Risks has been sitting on that investigation for fifteen months and for some reason has not issued a report about what happened to the veterans.

I would like to point out that I've never had another relapse. I simply take my medication everyday. If anyone told me to stop taking medication,

I wouldn't follow that advice. It was a terrifying and damaging experience.

People with schizophrenia suffer enough. The stigma of the illness frightens people. It is a very lonely life. I know. But those of us with schizophrenia really want the same things out of life that others want. We do need treatment that helps us to become the best that we can be. To deliberately harm us, without informed consent, is unconscionable. I told my father one evening when we went for a walk that I think I have half a life . . . but I do want to lead that half a life as fully as I can.

Sadly, even with the protocols showing that patients would be harmed by participation in the U.C.L.A. research, O.P.R.R. did not act promptly, as it should have. Over a period of three years, O.P.R.R. never interviewed a single patient in the U.C.L.A. program. This upsets me. The Office for Protection from Research Risks is saying to 107 subjects with schizophrenia, "You're worthless -- Tony, Elizabeth, Gabby, and the others who were harmed in this program. It's the researchers that really matter."

Mr. Chairman and Members of the Subcommittee, I have one message today. The system does not protect human subjects. It protects the researchers. New legislation is needed.

In closing, I wouldn't be here without deeply supportive family and their friends and the many experts who stood with us. Perhaps the researchers thought that the public would never find out what they were doing. But they were wrong. However, in spite of the evidence, just like the doctors at Tuskegee and the doctors who conducted radiation experiments, the UCLA doctors claim that they did nothing wrong.

I am grateful to you, Mr. Chairman and Members of the Subcommittee, for the rare opportunity to speak today.

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Prodromal Signs and Symptoms of Schizophrenic Relapse

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Six-week periods prior to 17 psychotic relapses and to 10 relapses characterized by depression and/or hostility were examined for 23 recent-onset schizophrenic outpatients. These prodromal periods were compared with periods that did not precede relapse for the same patients and for 27 schizophrenic patients who did not relapse. The Brief Psychiatric Rating Scale (BPRS) was used to assess symptomatology. Psychotic relapse was defined as an elevation to severe or extremely severe from nonpathological levels on one or more of the BPRS items: Hallucinations, Unusual Thought Content, and Conceptual Disorganization. Nonpsychotic relapses were similarly defined using the Depression and Hostility items of the BPRS. Even small elevations in odd thought content, unusual perceptual experiences, depression, somatic concern, and guilt above the levels usually present for a given patient may presage psychotic relapse during the 6 to 8 weeks prior to its occurrence. When compared with nonprodromal periods of other patients, periods before relapse were found to show significantly higher levels of hostility and grandiosity in addition to higher levels of unusual thought content and perceptual abnormalities. For relapses characterized by depression and hostility, an elevation of activation was found in the prodromal period.

Traditionally, the study of the symptoms of schizophrenia has focused on symptoms that occur in the floridly psychotic state. Only within the last two decades have the signs and symptoms prodromal to acute psychosis been systematically examined. This research has been stimulated by increasing evidence that decompensation into acute psychosis can often be avoided with active pharmacologic and psychosocial intervention at the early signs of relapse.

Docherty, Van Kammen, Siris, and Marder (1978) completed an extensive review of the early literature on prodromal features of schizophrenic relapse and found that almost all studies involved retrospective reports. Retrospective studies of the relapse process may involve a biased view of past events, as the negative outcome is known when data are collected. Three new studies have used prospective designs. We will comment briefly on each.

Herz, Szymanski, and Simon (1982) examined prodromal symptoms as part of a pilot study of an intermittent medication strategy for schizophrenic outpatients. Monitoring for the appearance of symptoms potentially prodromal to relapse was done in weekly group therapy sessions using the Problem Appraisal Scale and the Global Assessment Scale. Of the 10 patients who made it through the initial drug washout and into the intermittent medication protocol, 5 experienced an increase in nonpsychotic symptoms and were temporarily treated with neuroleptic medication. The symptoms typically observed were sleep disturbances, agitation, anxiety, anger, social withdrawal, and impaired social relations. It is not possible to know whether these mild elevations in symptomatology would have progressed to a full psychotic relapse. No statistical analyses were reported to indicate whether the elevations of these typical symptoms were significantly higher than for the nonrelapsers.

In the context of a targeted medication protocol, Heinrichs and Carpenter (1985) examined elevations in symptomatology thought to be prodromal to schizophrenic relapse (see Carpenter & Heinrichs, 1983, for a more detailed protocol description). In addition to 17 drug-free schizophrenic patients, a comparison group of 30 schizophrenic patients receiving maintenance neuroleptics was also included. When a decompensation was judged to have begun, the changes in signs and symptoms that the therapist thought had presaged the exacerbation were recorded. Again, prompt pharmacologic intervention prevents us from knowing whether all of these episodes of decompensation would have progressed to full psychotic relapse.

The data for the medicated and drug-free groups were combined because the groups differed on only one symptom con-

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Computing assistance was provided by the Data Management Unit of the University of California, Los Angeles, Clinical Research Center for the Study of Schizophrenia. Brief Psychiatric Rating Scale reliability training was supervised by the Diagnosis and Psychopathology Unit of the Clinical Research Center for the Study of Schizophrenia.

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struct, that of sleep disturbance. The 10 most common prodromal symptoms in order of their frequency were hallucinations, suspiciousness, change in sleep, anxiety, cognitive inefficiency, anger/hostility, somatic symptoms or delusions, thought disorder, disruptive inappropriate behavior, and depression. Unfortunately, the nonrelapsed patients were not statistically compared with the patients who relapsed.

Another recent prospective study of prodromal signs is provided by Marder et al. (1984). Forty-one chronic schizophrenic men were followed at an outpatient clinic and treated with fluphenazine decanoate administered every 2 weeks. The Brief Psychiatric Rating Scale (BPRS) interview (Overall & Gorham, 1962) and the Symptom Checklist 90 (SCL-90; Derogatis, Lipman, & Covi, 1973), a patient self-report scale, were administered at baseline, 2 weeks later, then monthly for 3 months, and then every 3 months. Relapse was defined as the failure of an increase in medication to manage symptoms following an exacerbation of BPRS psychosis or paranoia ratings. Fourteen of the patients relapsed. Marder et al. (1984) found elevations on the thought disorder, depression, and paranoia factors of the BPRS as well as on the interpersonal sensitivity, depression, anxiety, paranoid ideation, and psychoticism factors of the SCL-90 just prior to relapse. The most discriminating factors identified by a step-wise discriminant function analysis were the paranoia and depression factors from the BPRS and the psychoticism factor from the SCL-90. There were also some indications that anxiety, depression, and interpersonal sensitivity increased earlier than did BPRS thought disorder.

The present study is a prospective examination of prodromal signs and symptoms of schizophrenic relapse, using a systematic and carefully controlled research design. One important improvement over the previous studies is that relapse was defined as the elevation of psychiatric symptoms to the severe or extremely severe level. Thus, minor symptom fluctuations that might often be inconsequential were not considered relapses. In contrast to the studies that defined the period of observation by the necessity to increase medication to avoid a possible relapse, we can be certain that any prodromal changes that we isolated actually did precede a clear relapse. Another methodological improvement is that the use of reliable, systematic BPRS ratings every 2 weeks allowed us to follow the course of the prodrome from early signs all the way to relapse. This ensured that we were able to examine subtle changes in symptomatology that may portend the relapse.

In addition to psychotic relapses, this study also examined other relapses in schizophrenic patients, namely, those relapses involving either severe depression or hostility but not severe psychotic symptoms. This was done to determine whether some prodromal signs preceded psychotic relapse, as opposed to other types of relapse.

Finally, the present study focused on a nonchronic population, whereas the previous prospective studies have used older, chronic patients. The variability in illness course that characterizes recent-onset patients allows for distinct periods of remission followed by exacerbation of symptoms prodromal to relapse.

Following Marder et al. (1984), the present study used two types of comparisons. The 6-week period prior to the relapse period was compared with a 6-week period not preceding a relapse for the relapsing patients (within-patients comparison). In addition, the prodromal periods were compared to 6-week periods of symptomatology in patients who did not relapse (between-patients comparison). The within-patients comparison addresses the question of whether any specific symptoms become elevated, prior to relapse, over and above the levels usually present for these same patients. The between-patients comparison examines whether any symptoms occur at higher levels, during the prodromal periods, than those usually found among nonrelapsing patients.

Method

Subjects

Fifty schizophrenic patients who attended the University of California, Los Angeles, Aftercare Clinic served as subjects. Twenty-three patients relapsed a total of 27 times. Seventeen of the 27 relapses involved severe psychotic symptoms (psychotic relapses) and the other 10 involved severe depression and/or hostility (nonpsychotic relapses), with 4 patients having both a psychotic relapse and a nonpsychotic relapse on separate occasions. Another 27 patients served as nonrelapsed comparison subjects. The 4 patients with both types of relapses had separate nonrelapsed comparison patients for their psychotic and nonpsychotic relapses.[1]

The 50 schizophrenic subjects are participants in a larger longitudinal follow-through study of the early phase of schizophrenic disorders, entitled Developmental Processes in Schizophrenic Disorders (principal investigator: Keith H. Nuechterlein). These patients were required to have a diagnosis of schizophrenia or schizoaffective disorder, mainly schizophrenic, by Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) with the first psychotic episode occurring not longer than 2 years before project contact. Subjects with any of the following were excluded: (a) evidence of an organic central nervous system disorder (e.g., epilepsy); (b) significant and habitual drug or alcohol abuse in the 6 months prior to project intake, or clouding of the diagnostic picture by past drug or alcohol abuse; or (c) premorbid IQ less than 70. Please see Nuechterlein, Edell, Norris, and Dawson (1986) for a complete description of the selection criteria.

Of the 50 patients, 39 were men and 11 were women. Forty-one of the patients were given diagnoses of schizophrenia and the other 9 were diagnosed as schizoaffective, mainly schizophrenic. Forty-five patients were Caucasian, 4 were Hispanic, and 1 was of mixed heritage. The patients were relatively young (mean age at study entry = 23.4 years; SD = 3.4; range = 18–32 years) and had a mean total time of schizophrenic illness prior to admission to the clinic, including prodromal symptoms, of only 13.4 months (SD = 11.7; range = 1–48 months). The patients had completed an average of 12.3 years of school (SD = 2.2; range = 5–16 years). Mean social class level, as measured by the Amherst modification of Hollingshead's Two-Factor Index of Social Position (Watt, 1974), was 3.1 (SD = 1.3, range = 1–5). The mean interval from clinic admission to relapse for relapsing patients was 18.3 months (SD = 10.1; range = 2–37 months). There were no significant differences on the RDC diagnostic subtypes or on any of the demographic variables between the psychotic relapsers and their comparison patients, or between the nonpsychotic relapsers and their comparison patients.

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[1] Two additional nonpsychotic relapsers had a psychotic relapse at another time that was excluded by our criteria, and another two nonpsychotic relapsers at another time had moderate psychotic symptoms. Thus, on the whole, the course of the nonpsychotic relapsers also involved periods of psychosis.

The nonpsychotic relapsers were also no more likely to be RDC schizoaffective than were the psychotic relapsers.

Seven of the psychotic relapsers were on standardized maintenance neuroleptics (12.5 mg fluphenazine [Prolixin] decanoate every 2 weeks) as part of a research protocol, 6 were off medication completely, and 4 were on a combination of fluphenazine decanoate and/or another medication (e.g., an antidepressant) at time of relapse. During the periods used as within-patients comparison periods, 7 of the psychotic relapsers were on maintenance neuroleptics, 5 were drug-free, and 5 were on a combination of medications. Twelve of the nonrelapsed comparison patients were on maintenance neuroleptics, 2 were drug-free, and 3 were on a combination of medications.

Six of the relapses characterized by depression and/or hostility occurred while the patient was on maintenance neuroleptics, 1 during a drug-free period, and 3 during a period in which a combioation of medications was being administered. During within-patients comparison periods, 6 of the nonpsychotic relapsers were on maintenance neuroleptics, 1 was drug-free, and 3 were on a combination of medications. Seven of the comparison patients were on maintenance neuroleptics, 1 was drug-free, and 2 were on a combination of medications. The patients in this study who were drug-free were in a drug withdrawal phase of a research protocol, which was offered to patients who showed reasonable clinical stability during their first outpatient year on maiotenoance neuroleptics.

Procedure

The BPRS (Overall & Gorham, 1962) was rated based on a brief, semistructured clinical interview intended for this purpose, which was administered every other week as part of the patients' meetings with their case managers. Each BPRS covered the preceding 2 weeks. The professional training of the case managers included one PhD and two MAs in psychology and two MSWs. Case managers completed structured training in BPRS rating using taped and live interviews, and demonstrated mean iotraclass reliability across scales of .77 to .93, with a mean of .85. The BPRS consists of 18 psychiatric symptom constructs. Each item is rated on a 7-point scale, using a BPRS version with clearly specified criteria for each item (Lukoff, Nuechterlein, & Ventura, 1986). Thus, this assessment iostrument is particularly suited for measuring patient change. Five factors—Thought Disturbance, Anergia, Anxiety-Depression, Hostile-Suspiciousness, and Activation—have been derived from these 18 items by Guy (1976) to examine separate symptom dimensions. The mean of the 18 individual items was used as a measure of overall symptomatology.

Psychotic relapse was defined as a rating of 6 or 7 (severe or extremely severe) on the Unusual Thought Content, Hallucinations, or Conceptual Disorganization items of the BPRS. Nonpsychotic relapse was defined as a rating of 6 or 7 (severe or extremely severe) on the BPRS items of Depression or Hostility. For our purposes, relapses were not included if they followed a prior relapse without a return to a moderate level (4), or lower, for at least 3 months. Five patients could not be included io this study because their symptoms never adequately returned to a moderate level following project entry. To be certain that the nonpsychotic relapses were not merely early phases of a psychotic relapse, the nonpsychotic relapses were restricted to those that were not followed by a psychotic relapse for at least 3 months. A further indication that increases in psychotic symptoms were not of primary concern on these occasions is that in only 3 of the 10 nonpsychotic relapses were antipsychotic medications reinstated or increased at the time of relapse. If a patient relapsed more than once while he or she attended the clinic, we selected the prodromal period for which data points were available for each 2-week period and, if possible, one during which the patient was on standardized protocol medication.

For each patient who relapsed, a period not preceding relapse was identified for use as a within-patients comparison. If an appropriate comparison period was not available, the patient was not included in the study. To discriminate these periods from relapse periods, a 6-week period was chosen that contained no ratings of 5 or above on any of the five relapse scales and for which a 5 did not occur on any relapse scale for at least 2 following months. Again, if more than one period was available, periods for which data points were not available for each 2-week period were excluded. If periods longer than 6 weeks occurred, the first and then the last months were dropped so as to cut the length of the period to 6 weeks. In the case of more than one appropriate comparison period, the period during which medications were most similar in type and dosage to that of the prodromal period was used. After these criteria, we selected the comparison period that helped to equate the ratio between comparison periods that follow the prodrome and those that precede the prodrome. Separate within-patients comparison periods for psychotic and nonpsychotic relapses were selected for the 4 patients with one relapse of each type.

The between-patients comparison periods were obtained from the remainder of the patients who had obtained relative choical stability and had not relapsed. The period was identified in the same manner as the within-patients comparison. Seventeen periods from the nonrelapsing patients were selected for comparison with the 17 psychotic relapsers and an additional 10 comparison periods were selected for comparison with the nonpsychotic relapsers. Assignment of patients to comparison groups attempted to equate as closely as possible the relapse and comparison groups with respect to type and dosage of medications and time since admission to the clinic. The distribution of medication status did not differ significantly across relapse and comparisoo groups, nor were there statistically significant differences in time since admission to the clinic (at the time of relapse or, for nonrelapsers, the end of the comparison period) between the relapsers and their respective comparison groups.

Results

Statistical Approach

To avoid excessive Type I error, the following strategy was implemented for the data analyses. The BPRS mean psychopathology score was examined initially to evaluate overall differences between prodromal and comparison periods. The BPRS factor scores (Guy, 1976) were then entered into a repeated measures analysis of variance in order to determine if differences between prodromal and comparison periods were greater on some factor scores than others. If the interaction between period (prodrome, comparison) and BPRS factor scores was statistically significant, individual BPRS factor scores were examined to determine which of the factors discriminated significantly between prodromal and comparison periods. The BPRS items that load on a factor were examined only if the corresponding factor score showed significant discrimination. *F* tests with conservative degrees of freedom were used to evaluate all repeated-measure effects following Greenhouse-Geisser (Winer, 1971).

Psychotic Relapse

Seventeen psychotic relapses were examined, 8 of which were relapses on BPRS Unusual Thought Content, 3 on BPRS Hallucinations, and 6 on both Unusual Thought Content and Hallucinations. No relapses met the full inclusion criterion based on the BPRS Conceptual Disorganization scale.

Separation of relapse and comparison points. Effect size was computed for each of the five BPRS items used as relapse criteria between the relapse point (Weeks 0 and 1) and the corresponding point (Weeks 0 and 1) for the within-patient comparisons, to illustrate the degree of separation created at this point by the group-defining criteria. This BPRS is referred to as covering Weeks 0 and 1 because the symptomatology that met relapse criteria could have begun at any point during the 2-week period covered by this rating point. Cohen's *d* (Cohen, 1969), which scales the separation of means in standard deviation units, was used as the effect size measure. The psychotic relapse and within-patient comparison points were successfully separated by the defining criteria as evidenced by the effect sizes for both Hallucinations (d = 1.67, Ms = 4.06 and 1.24, respectively) and Unusual Thought Content (d = 3.21, Ms = 5.53 and 1.59). Depression also distinguished the two points d = 1.15, Ms = 3.53 and 1.71). The effect size for Conceptual Disorganization was smaller (d = .73, Ms = 1.82 and 1.06).

Effect size was also computed for each of the five BPRS items used as relapse criteria between the psychotic relapse point (Weeks 0 and 1) for the 17 relapsing patients and the corresponding point of the between-patient comparison periods for the 17 nonrelapsers. The defining criteria for relapse and nonrelapse points led to notable separations on Unusual Thought Content (d = 4.56, Ms = 5.53 and 1.12, respectively), Hallucinations (d = 1.71, Ms = 4.06 and 1.18), and Conceptual Disorganization (d = .79, Ms = 1.82 and 1.00). In addition, the psychotic relapse point included somewhat more Depression (d = 1.70, Ms = 3.53 and 1.53, respectively) and Hostility (d = .93, Ms = 1.94 and 1.18) than the nonrelapse point.

Within-patients comparison. To examine prodromal symptoms through a within-patients comparison, a 2 × 3 analysis of variance (ANOVA) was computed for the BPRS mean psychopathology score with period (prodrome, comparison) and week (the 2-week blocks ending 6, 4, and 2 weeks prior to the BPRS interview at the relapse or "0" point) as repeated-measure variables. The overall symptomatology level was higher for the patients during the 6 weeks prior to relapse than during the periods that had not preceded a relapse (BPRS mean psychopathology score period effect, $F(1, 16) = 7.68$, $p < .02$). See Table 1 for means and standard deviations for this effect and all other significant period effects for psychotic relapses. Then period (prodrome, comparison), week (6, 4, and 2 weeks prior to the relapse or 0 point BPRS interview), and BPRS factor score (Thought Disturbance, Anergia, Anxiety-Depression, Hostile-Suspiciousness, Activation) were examined in a 2 × 3 × 5 repeated-measure ANOVA. A significant interaction between period and BPRS factor score, $F(3.1; 48.9) = 7.61$, $p < .001$, indicated that BPRS factor scores were differentially elevated between prodrome and comparison periods. Also significant were main effects of period, $F(1, 16) = 7.34$, $p < .02$, and BPRS factor score, $F(2.2, 35.5) = 4.04$, $p < .03$.[2]

Given that the Period × BPRS Factor Score interaction was significant, the individual factor scores were then examined to determine which factors significantly distinguished between the relapse and comparison periods. Period (prodrome, comparison) and week (6, 4, and 2) were examined as repeated-measure variables in a 2 × 3 ANOVA for this purpose. The BPRS Anxiety-Depression factor, $F(1, 16) = 12.74$, $p < .003$, and the BPRS Thought Disturbance factor, $F(1, 16) = 8.97$, $p < .009$, were elevated during the prodromal period. In addition to these period effects, a week effect for the BPRS Thought Disturbance factor, $F(1.52, 24.31) = 5.28$, $p < .02$, reflected an increase in thought disorder during Weeks 2 to 4 of both the prodrome and the comparison period.

Table 1
Mean Brief Psychiatric Rating Scale (BPRS) Scores for Psychotic Prodromes and Comparison Periods

	6-week periods					
	Prodrome		Within-patients comparison		Between-patients comparison	
BPRS scores	*M*	*SD*	*M*	*SD*	*M*	*SD*
Overall BPRS *M*	1.57	0.38	1.34*	0.23	1.37*	0.21
Factors						
Anxiety-Depression	1.90	0.83	1.38**	0.44		
Thought Disturbance	1.57	0.70	1.12**	0.30	1.07**	0.21
Hostile-Suspiciousness	1.44	0.50			1.12*	0.21
Individual items						
Somatic Concern	1.82	1.18	1.25*	0.59		
Depression	2.16	1.24	1.37**	0.69		
Guilt	1.45	0.83	1.14*	0.35		
Hostility	1.80	1.00			1.25*	0.56
Unusual Thought Content	2.04	1.43	1.33*	0.91	1.18**	0.59
Grandiosity	1.22	0.58			1.00*	0.00
Hallucinations	1.80	1.50	1.02*	0.14	1.10*	0.50

* $p < .05$, compared with the prodromal period, analysis of variance period effect.
** $p < .01$, compared with the prodromal period, analysis of variance period effect.

Analyses of variance were computed for each of the individual BPRS items that contribute to the Anxiety-Depression and Thought Disturbance factor scores to determine the individual symptom constructs that significantly separate prodromal and within-patients comparison periods. The BPRS Anxiety-Depression factor items of Depression, Guilt, and Somatic Concern were significantly elevated prior to psychotic relapse as compared with periods not prodromal to relapse for the same patients, whereas anxiety was not. See Table 2 for F ratios and significance levels of the period effects for the individual BPRS items for the psychotic prodromes.

The items of the BPRS Thought Disturbance factor that were significantly elevated during the prodrome as compared with the control period were Uousual Thought Content and Hallucinations. As noted earlier, these were also the psychotic relapse criterion items on whicb relapses occurred.

[2] To determine the impact of the four patients in the psychotic prodrome group who also were included in the nonpsychotic relapse group, this ANOVA was rerun excluding these overlapping patients. The results paralleled closely the findings for the full 17 patients. We also determined that eliminating the Research Diagnostic Criteria schizoaffective, mainly schizophrenic, patients did not change the level of statistical significance for any of the key effects involving period and factor.

Table 2
Analysis of Variance Period Effect Statistics for Brief Psychiatric Rating Scale Individual Items for Psychotic Prodromes

Item	Comparison	
	Within-patients	Between-patients
Somatic Concern	$F(1, 16) = 5.44$, $p < .04$	
Depression	$F(1, 16) = 14.50$, $p < .002$	
Guilt	$F(1, 16) = 6.90$, $p < .02$	
Hostility		$F(1, 32) = 5.63$, $p < .03$
Unusual Thought Content	$F(1, 16) = 5.99$, $p < .03$	$F(1, 32) = 10.01$, $p < .004$
Grandiosity		$F(1, 32) = 7.17$, $p < .02$
Hallucinations	$F(1, 16) = 5.62$, $p < .04$	$F(1, 32) = 4.46$, $p < .05$

Between-patients comparison. The between-patients comparison was used to determine whether the within-patients prodromal findings would generalize to differences between patients who relapsed and those who did not relapse. Analyses of variance were computed for the BPRS mean psychopathology score with period (prodrome, comparison) as a between-patients variable and week (the 2-week blocks ending 6, 4, and 2 weeks prior to the relapse or 0 point) as a repeated measure. The overall symptomatology level was significantly higher prior to psychotic relapse than during the nonrelapsers' comparison period (BPRS mean psychopathology score period effect), $F(1, 32) = 4.83$, $p < .04$. See Table 1 for the means and standard deviations for significant period effects in this section.

An ANOVA was computed with period (prodrome, comparison) as a between-patients variable and week (6, 4, and 2 weeks prior to the relapse BPRS interview) and BPRS factor score as repeated measures. A significant interaction between period and BPRS factor score, $F(2.5, 81.4) = 3.58$, $p < .03$, indicated that BPRS factor scores were again differentially elevated between prodrome and comparison periods. Main effects of period, $F(1, 32) = 5.14$, $p < .04$, and BPRS factor score, $F(2.5, 81.4) = 3.58$, $p < .03$, were also significant.[3]

Given that the BPRS factor scores were differentially elevated, a 2 (period) × 3 (week) ANOVA was computed for each BPRS factor score to determine which factors discriminated significantly between prodrome and comparison periods. The two BPRS factors that were significantly higher in the prodromal period than in the nonrelapsers' comparison period were Thought Disturbance: period effect $F(1, 32) = 12.01$, $p < .002$, Period × Week interaction $F(1.46, 46.99) = 5.54$, $p < .02$; and Hostile-Suspiciousness: period effect $F(1, 32) = 7.44$, $p < .02$. The Thought Disturbance interaction reflected a slight decrease 4 weeks before relapse and a small rise 2 weeks before relapse relative to the comparison period.

Three of the four symptom scales contributing to the Thought Disturbance factor, namely Unusual Thought Content, Hallucinations, and Grandiosity, were significantly elevated during the prodromes relative to the between-patients comparison period (see Table 2). For Unusual Thought Content a Period × Week interaction, $F(1.46, 46.71) = 4.72$, $p < .03$, reflected a slight decrease 4 weeks before relapse followed by a moderate increase 2 weeks before relapse that did not characterize the nonrelapsing patients. For the BPRS Hostile-Suspiciousness factor, the Hostility item was significantly elevated (period effect).

Discriminant analysis of psychotic relapses. A discriminant analysis was computed using all five BPRS factor scores during the period 6 to 8 weeks prior to relapse to determine if early prodromal periods can be distinguished from comparison periods of nonrelapsing patients. A step-wise procedure was used with *F*-to-enter set at 2.1 and *F*-to-remove at 2.0. Two factors contributed to the discrimination, BPRS Hostile-Suspiciousness, $F(1, 31) = 3.66$, and BPRS Thought Disturbance, $F(1, 31) = 2.16$. The overall predictive model was significant, $F(2, 31) = 3.91$, $p < .05$. This model correctly classified 10 of the 17 prodromal periods (58.8%) and 15 of the 17 comparison periods (88.2%) for a total correct classification rate of 73.5%. Lachenbruch and Mickey's (1968) jackknife procedure reduced correct classifications only slightly (70.6%). Classification of prodromal periods continued to be correct for 58.8% of the relapsing cases. However, classification of control periods fell slightly to 82.4%.

Differences between comparison groups. To determine if the relapsing patients differed from nonrelapsing patients even when the former were not in a prodromal period, within-patients and between-patients comparison periods were contrasted. An ANOVA was computed for each BPRS factor with comparison period (within, between) as a between-groups variable and week (6, 4, and 2 weeks prior to the BPRS interview at point 0) as a repeated measure. In general, no significant differences were found. One Period × Week interaction effect occurred for the Thought Disturbance factor, $F(1.7, 54.8) = 4.74$, $p < .02$, reflecting extremely small initial changes in values, in opposite directions, which had no apparent effect on the interpretation of the interaction effect for this factor that involved prodromal and between-patients comparison periods. No significant effects were found for the individual items of the Thought Disturbance factor.

Depression and Hostility Relapses

Ten relapses that involved mainly nonpsychotic symptoms were examined: 6 relapses on the BPRS Depression scale, 3 relapses on the Hostility scale, and 1 relapse on both Depression and Hostility.

Separation of relapse and comparison points. Measures of effect size were computed for each of the five BPRS items used as relapse criteria between the nonpsychotic relapse points and the correspoonding points for the within-patients comparison periods. The relapse and comparison points were notably sepa-

[3] As for the within-patients comparison, this ANOVA was rerun excluding the four patients who also were included in the nonpsychotic relapse group. Similarly, we reran this ANOVA without the schizoaffective, mainly schizophrenic, patients. The significance levels of the key effects did not change.

rated by the defining criteria, as shown by effect sizes for Depression (d = 2.03, Ms = 4.70 and 1.50, respectively) and Hostility (d = 1.05, Ms = 3.50 and 1.60). The relapse point was also characterized by somewhat more Unusual Thought Content (d = .71, Ms = 2.30 and 1.30) and Hallucinations (d = .75, Ms = 2.40 and 1.10) than the comparison point. Thus, although these relapses were characterized by predominance of severe depression or hostility, some increase in mild psychotic symptoms is also suggested.

Effect size was also computed for each of the five BPRS items used as a relapse criterion between the nonpsychotic relapse point for the 10 relapsing patients and the corresponding point of the between-patients comparison periods for the 10 nonrelapsers. The two points were separated by the relapse defining criteria scales of Depression (d = 1.71, Ms = 4.70 and 1.80, respectively) and Hostility (d = 1.22, Ms = 3.50 and 1.30). In addition, a smaller separation of these points was noted for Hallucinations (d = .99, Ms = 2.40 and 1.10).

Within-patients comparison. To examine prodromal symptoms, ANOVAs were computed for the BPRS mean psychopathology score with period (prodrome, comparison) and week (the two-week blocks ending 6, 4, and 2 weeks prior to the BPRS interview at the relapse or 0 point) as repeated measures. Effects for the mean psychopathology score were not significant. Before proceeding with the analysis of the individual BPRS factor scores, an ANOVA was computed with period (prodrome, comparison), week (6, 4, and 2), and BPRS factor score as repeated-measure factors, to examine whether the pattern of BPRS factor scores differed between the prodrome and comparison periods. This was verified by the significant Period × BPRS Factor Score interaction effect, $F(2.2, 19.6) = 3.89$, $p < .04$. A significant main effect of BPRS factor score, $F(2.0, 18.1) = 4.5$, $p < .03$, was also present. The levels of significance of the key effects did not change when the ANOVA was rerun without the schizoaffective, mainly schizophrenic, patients.

To determine which BPRS factor scores significantly distinguished between the prodromal and comparison periods in the above Period × BPRS Factor Score interaction, ANOVAs were computed for each BPRS factor score with period (prodrome, comparison) and week (6, 4, and 2 weeks prior to the relapse BPRS or 0 point) as repeated measures. The BPRS Activation factor score, $F(1, 9) = 5.92$, $p < .04$, was elevated during the prodrome as compared with the control period (M = 1.41, SD = .47, and M = 1.17, SD = .26, respectively). However, none of the individual BPRS symptom items that load on the BPRS Activation factor (Excitement, Tension, and Mannerisms and Posturing) were significantly elevated during the prodromal period for nonpsychotic relapses.

Between-patients comparison The following between-patients comparisons were made in order to determine whether the within-patients prodromal findings for nonpsychotic relapses would generalize to comparisons with patients who had not relapsed. A 2 (period) × 3 (week) repeated-measure ANOVA was computed for the BPRS mean psychopathology score. No significant effects were observed. Consistent with the data analysis strategy, a 2 (period) × 3 (week) × 5 (BPRS factor score) ANOVA was computed. Only the main effect for BPRS factor was significant, $F(1.96, 35.29) = 35.29$, $p < .003$. Because the Period × BPRS Factor Score interaction was not significant, BPRS factor scores were not further analyzed for the between-patients comparison.

Discussion

The major finding of this study is that there are identifiable prodromal symptoms and signs of psychotic relapse for schizophrenic patients. To a much lesser extent, such prodromal features are evident for relapses in schizophrenic patients that are characterized by severe depression or hostility.

Overall symptomatology was increased during the 6 weeks preceding psychotic relapse in comparison to periods that did not precede relapse for the same patients (within-patients comparison). These elevations occurred mostly for the symptoms that load on the Thought Disturbance and Anxiety-Depression factors of the BPRS. Higher ratings on the BPRS Unusual Thought Content scale and Hallucinations scale during the prodrome often involved subtle increases in quasipsychotic phenomena that did not impair functioning, as opposed to the persistent and impairing psychotic symptoms that defined psychotic relapse. Also significantly elevated during the prodrome were symptoms measured by the BPRS items of Depression, Somatic Concern, and Guilt, again often at a relatively mild level of severity. Thus, a combination of lower level psychotic and nonpsychotic symptoms presaged relapses that were characterized by very severe psychotic symptoms.

A somewhat different set of signs prodromal to psychotic relapse became apparent in comparison with patients who did not relapse (between-patients comparison). Small increases in strange thought content and unusual perceptual experiences again distinguished the prodromal periods. However, depression, guilt, and somatic concern were no longer significantly elevated in the prodromal period relative to the comparison period. Thus, these last three symptoms were increased in the prerelapse period relative to the levels existing during nonrelapsing periods of the same patients, but were not significantly higher than the levels shown by nonrelapsing schizophrenic patients.

In the between-patients analysis, in addition to elevations in low level cognitive and perceptual abnormalities related to delusions and hallucinations prior to relapse, there were increases in BPRS Hostility and BPRS Grandiosity. These symptoms were not elevated in the within-patients comparison and are not psychotic symptoms per se. However, they often accompany paranoid ideation. These findings suggest that hostile, grandiose symptoms may characterize schizophrenic patients who are likely to show severe psychotic relapses, but that these symptoms do not increase significantly just before such relapses.

Increases in odd thought content became much more prominent in the period 2 to 4 weeks prior to the psychotic relapse point, relative to the between-patients comparison periods. This is concordant with Marder et al.'s (1984) finding that worsening on the BPRS Thought Disorder factor occurred only within 4 weeks of relapse.

The results of this study are in partial agreement with the three previous empirical prospective studies of schizophrenic decompensation (Heinrichs & Carpenter, 1985; Herz et al., 1982; Marder et al., 1984). Elevations in hostility and suspiciousness were found in the psychotic prodromes in all three earlier studies. In addition, anxious depression and thought dis-

turbance were significantly elevated, as reported in the two latter studies that included adequate nonrelapsing controls. The present findings did not confirm the presence of anxiety as found in these previous studies. Although the BPRS Anxiety-Depression factor was significantly elevated for the within-patients comparison, the individual BPRS Anxiety item was not significantly elevated. One of these three previous studies (Marder et al., 1984) used psychotic exacerbation as the relapse definition; the other two defined relapse as the appearance of symptoms judged to be prodromal to a schizophrenic episode. Thus, many of the symptom exacerbations in Herz et al.'s (1982) and Heinrichs and Carpenter's (1985) studies may not have proceeded to psychotic relapse as defined here. Perhaps anxiety is more characteristic of general exacerbation among schizophrenic patients, and is not prodromal to psychotic relapse. Change in sleep, which was reported in two of the earlier prospective studies (Heinrichs & Carpenter, 1985; Herz et al., 1982), was not measured in the present study.

The mean elevations in the prodromal symptoms reported in this study are small, on the order of 0.5 to 1 point on a 7-point scale. An inspection of the raw data revealed that typical elevations were slightly larger. For three patients virtually no prodromal symptoms were evident in the BPRS factor scores in the periods preceding psychotic relapse. Several additional patients did not begin to show any symptomatic changes until 2 to 4 weeks prior to the relapse. Thus, these patients lowered the magnitude of the mean elevations during the psychotic prodromal periods. However, the typical elevations during the identifiable individual prodromal periods were also relatively small. Given that patients varied in the length of time taken to decompensate, we may be examining prerelapse symptoms for the quick relapsers and the early component of relapse for the patients whose symptoms increased more gradually to relapse levels. We choose to call this 6-week period a prodromal period because we define relapse as the reoccurrence of severe psychotic symptoms, but recognize that some investigators might view even the return of mild psychotic phenomena as a relapse. One strength of the present approach is that we are certain that the symptoms we examined actually were prodromal to a psychotic relapse, not merely judged to be signs of an impending relapse that presumably would have occurred if not aborted through pharmacologic intervention. Our results suggest that schizophrenic patients should be closely monitored for even small prodromal changes in the symptoms reported here, as they are specific to clear relapse.

To determine if relapse could be predicted as early as 6 to 8 weeks prior to its occurrence, the five BPRS factor scores from that period were entered into a discriminant analysis of the psychotic prodromes and the corresponding comparison periods of the nonrelapsing patients. The Hostile-Suspiciousness and Thought Disturbance factors contributed to the best discrimination of relapse and nonrelapse periods. This discrimination was specific, but not highly sensitive.

For clinical purposes, it would be helpful to know whether prodromal changes might be detectable from within-patients changes. As a preliminary exploration of this issue, we examined week-to-week changes in the two factors that were significantly elevated in the prodromal period relative to the within-patient comparison period. We noted that 12 of the 17 psychotic relapses (70.6% sensitivity) were preceded by an increase of any size in the Thought Disturbance factor score for the BPRS covering the period 2 to 4 weeks prior to relapse. A similar increase in this factor occurred in only 2 of the 17 within-patients control periods (88.2% specificity). The overall classification rate was 79.4%. Thus, in an exploratory analysis of this sample, we found that any increase in the BPRS Thought Disturbance factor seems to be highly predictive of a psychotic relapse within the next 4 weeks. Larger samples will be required to examine this issue further. Additional research could also help to determine whether the false positive rate for psychotic relapse prediction is higher than that found for the comparison periods examined here.

The findings for the depression and hostility relapses revealed that only one of the five BPRS factors, Activation, was significantly elevated during the prodromes for the within-patients comparison. BPRS factor scores during the nonpsychotic prodromes were not differentially elevated relative to the between-patient comparison periods. Thus, in keeping with our data analysis strategy, the BPRS factor scores for the between-patients comparison were not examined further. It is noteworthy that increases in depression and hostility were statistically significant for the psychotic prodromes but not for the nonpsychotic prodromes.

In conclusion, we have found that the appearance or worsening of low-level odd thought content, unusual perceptual experiences, depression, somatic concern, or guilt precede full psychotic relapse among schizophrenic patients by as long as 6 to 8 weeks. Even mild elevations in these symptoms above the levels usually present for a given patient may portend psychotic relapse. At 6 to 8 weeks prior to psychotic relapse, the presence of increased hostile-suspiciousness and thought disturbance were the most powerful predictors. Compared to schizophrenic patients who did not relapse, relapsing patients were also characterized by significantly higher levels of hostility and grandiosity in the prodromal period.

For nonpsychotic relapses in schizophrenic patients that involve severe depression or hostility, an elevation of activation was found in the prodromal period. Thus, not only was increased activation apparent as long as 6 to 8 weeks before relapse, but this symptom was specific to the prodrome of nonpsychotic relapses as opposed to that of psychotic relapses.

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Split of *JCCP*—New Section on Assessment

Beginning in 1989, APA will publish the *Journal of Consulting and Clinical Psychology* (*JCCP*) in two sections, one focusing on the traditional domain and one concentrating on the growing area of psychological assessment. Alan E. Kazdin, the current editor, will serve as the editor for both sections in 1989. *JCCP* will continue to be published on a bimonthly basis but will contain up to 1,200 pages per year, an anticipated increase in size of over 40%. The new section, *Psychological Assessment: A Journal of Consulting and Clinical Psychology,* will be published as a separate publication in 1989, with an additional 500 pages in four issues.

Assessment Journal—Editorial Policy Statement

Psychological Assessment: A Journal of Consulting and Clinical Psychology publishes mainly empirical papers concerning clinical assessment and evaluation. Papers that fall within the publication domain include investigations related to the development, validation, and evaluation of assessment techniques. Diverse modalities (e.g., cognitive, motoric) and methods of assessment (e.g., inventories, interviews, direct observations, psychophysiological measures) are within the domain of the journal especially as they are evaluated in clinical research or practice. Also included are assessment topics that emerge in the context of cross-cultural, ethnic, and minority issues. Case studies occasionally will be considered if they identify novel assessment techniques that permit evaluation of the nature, course, or treatment of clinical dysfunction. Nonempirical papers including highly focused reviews and methodological papers are considered if they facilitate interpretation and valuation of specific assessment techniques. Authors wishing to submit to the assessment section should send manuscripts to

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Testimony Presented Before
the Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Technology

Washington D.C.

May 23, 1994

By
Frank R. Palin, B.S.N., M.A.

Running Head: TESTIMONY

Testimony before the Small Business Subcommittee
on Regulation, Business Opportunities, and Technology

My name is Frank R. Palin. I am an emergency room technician at Rhode Island Hospital. I have received a Bachelor of Science in Nursing and a Master of Arts in Chemical Dependency Counseling this past weekend from Rhode Island College. My background also includes a Bachelor of Science in Business Management from Providence College, seven years business experience with International Business Machines Corporation and ten years as a small business owner. Four years ago, I decided to make a career change and to pursue a nursing career.

My duties as an emergency room technician include assisting the doctors and nurses in the trauma rooms, triage, urgent patient treatment area, and in pediatrics. An emergency room technician does vital signs, EKGs, draws blood, starts intravenous lines, inserts foley catheters, assists in restraining patients and performs any other tasks in the department as ordered.

My background in philosophy and ethics is longstanding. My high school education at St. Raphael Academy included Aquinas philosophy. This instruction continued with fifteen credit hours of philosophy and ethics at Providence College. During the past twenty years, I have read many twentieth century historical books. Repeated instances of human rights violations are described within this century. Atrocities committed by the Nazis during World War II "research" are particularly offensive. (Shirer, 1960) The issue of informed consent has been included as a key portion of the medical ethics component of my nursing studies at Rhode Island College. The faculty, in the Department of Nursing, provided me with a solid educational foundation in medical ethics and informed consent. This background allowed me to take a strong stand on this important issue.

Research on human subjects plays an integral part in conquering new frontiers in health care. The continuing abuses of ethical guidelines by callous researchers threaten the continuance of future human subject investigations. The atrocities of human subject experimentation by the Nazis in World War II led to the Nuremberg Code. (Annas, 1992, Annas & Grodin, 1992, Beauchamp & Childress, 1989, Greenwald, Ryan & Mulvihill, 1982, Jones, 1981, Robison & Pritchard, 1979) The Tuskegee Syphilis Study (Annas & Grodin, 1992, Greenwald, Ryan & Mulvihill, 1982, Jones, 1981) is an example of a grave abuse that took place here in the United States. Recent disclosures of radiation testing with uninformed subjects is another example of the paternalistic attitude of researchers. (Mann, 1994 and Schneider, 1994) Human subject experimentation without informed consent continues to take place every day. (Kim & Spivey, 1994) The public needs the protection of strong unambiguous laws to prevent the continuation of abusive research.

I have been invited to appear before this subcommittee to provide an illustration of an abuse of human subject research that ignored informed consent and took advantage of a disadvantaged population. The study described below was chosen because of my intimate involvement in halting the process. I will attempt to convey a first hand narrative of my activities as a patient advocate to protect this impaired population.

I first became aware of Rhode Island Hospital's human subject research study on alcoholics and hypoglycemia on October 18, 1993. A memo dated October 12, 1993 from Dr. Andrew Sucov (Exhibit A) was attached to the Emergency Department payroll checks.

According to Dr. Sucov's memo (Exhibit A), the study was to focus on the "population of intoxicated patients, to see if they get hypoglycemic while in our care." The patients will have blood drawn on arrival and have "repeat

alcohol and glucose levels drawn at four hours and eight hours after arrival." Additionally, patients were not to be fed during the eight hour analysis period. Lab slips indicated that the blood work was to be billed manually rather than by computer. It was anticipated that the study would last approximately three months and include 300 patients.

The issue of informed consent came to mind immediately. An intoxicated patient cannot give informed consent. (Beauchamp & Childress, 1989, Robison & Pritchard, 1979)

The majority of patients to be included in this study are transported to the hospital by police or emergency medical service. They are individuals who are found publicly intoxicated and are required by federal decriminalization of alcoholism law (---cite law---) to be brought to a detoxification facility or an emergency room. The remainder of subjects are individuals who came to the emergency department for treatment of an injury and are held due to their intoxification. Many of the above patients suffer from mental illness, alcoholism or drug addiction and are protected by the American Disabilities Act. (Tucker & Goldstein, 1993)

The patients held for observation are kept in two constant observation rooms (referred to as "the tank" by staff) which are guarded by uniformed security personnel. Emergency room protocol (Exhibit B) necessitates that any patient who is noncompliant to the constant observation rooms' rules will be placed in four point restraints. This means that the patient's wrists and ankles will be tied with heavy leather restraining cuffs which are lashed to the stretcher. Documentation cites that, "the patient was restrained to protect self or others from injury." The reality of this situation usually is that the patient refused to have their blood drawn and the emergency room technician or nurse was ordered to draw the blood without

The Alcohol Study Timeline (Exhibit C) was posted on October 29, 1993. A paragraph within this document states: "Patients can not refuse to be part of this study, as they are technically not capable of refusing life-saving care while intoxicated." After reading this document , I spoke to my immediate supervisor, Catherine Fanning, R.N., A.C.M. about the refusal of the hospital to acknowledge the civil rights of the patient in regard to informed consent. I told her that "I would be unable to participate in the study by drawing blood because it would be against my ethical, moral and religious principles to violate the rights of a patient in this manner." She informed me that this study was part of the emergency department standards of practice and I could be reprimanded if I refused to follow these standards. She suggested that I speak with Dr. Sucov, Dr. Robert Woolard or Dr. Ludi Jagminis.

First thing Monday morning, November 1st, the following message was left for Drs. Woolard, Jagminis and Sucov: "Please postpone the commencement of the alcoholic hypoglycemia study until I have the opportunity to discuss the ethical considerations of the lack informed consent with you." I also left a message requesting assistance for Linda St. Angelo, R.N., Director of Emergency Nursing.

A telephone call was received early in the afternoon of November 1st from Mrs. St. Angelo. My concerns about the ethical issues involved within the study and my refusal to participate on ethical, moral and religious grounds, were discussed. I was told that: "The study will not be postponed and the doctors would talk to you only as a courtesy, if their schedules allowed." Mrs. St. Angelo also instructed me that this study was part of department standards. She stated: "Your failure to draw blood from a patient in this study could be considered insubordinate. I suggest that you carefully consider your decision and how it will affect your future." I requested documentation of the

consent. The patient is not discharged or allowed to leave the emergency department until their blood alcohol level reaches .10 or a responsible adult will sign the patient out. This patient is effectively incarcerated until sober.

Dr. Sucov presided over an inservice training session concerning this study on October 24, 1993. He reiterated the study protocol described within his October 12th memo. (Exhibit A) During the question and answer session at the end of the inservice, I asked if there had been any similar studies concerning hypoglycemia and alcoholics. He stated that, "there have been no similar studies but I feel that we may be mistreating our patients if it proves that they become hypoglycemic in our care." I then brought up my discomfort with the lack of informed consent within the protocol. His response was, "a patient cannot refuse life saving care." I questioned his definition of life saving care and he claimed that, "this study falls within the definition of life-saving care." When I realized that this direction in the conversation was not working, I suggested two alternatives which I felt would satisfy the ethical considerations of informed consent. My first suggestion was to wait until the patient was legally sober (.10 blood alcohol level) and ask for voluntary participation with a blood sample. This format was rejected. My second suggestion was for a more controlled version of the study. Recruit patients who are treated in the emergency room for intoxification as they are discharged and sober. Offer a stipend for those individuals who are willing to report to a test center and stay for a stipulated period of time. This group would receive a meal and not be allowed to drink for a specified time. Then all members of the study would be given measured amounts of an alcoholic beverage. Periodic blood work would be performed during the sobering up period. This suggestion was also rejected and Dr. Sucov ended the conversation.

department standards relating to this study and Mrs. St. Angelo forwarded a copy of the Institutional Review Boards permission to conduct the hypoglycemia study. (Exhibit D)

A review of the Rhode Island Hospital Employee Handbook (1991) states, "Critical offense violations of personal conduct that justify immediate discharge without regard to the employee's length of service or prior record of conduct" and continues with a list of critical offense violations that includes, "Insubordinate acts or statements or failure to carry out orders." I considered Mrs. St. Angelo's comments on insubordination a threat to fire me, if I failed to participate in this illegal and unethical study.

I quickly composed a letter (exhibit E) which stated, "the civil liberties of an indigent population within this community are possibly being violated by Rhode Island Hospital, Brown University and three physicians and Brown faculty members." The letter continues with complaints about a lack of informed consent and that "the patient cannot refuse to be part of this study." Mention of body fluids being removed from the patients without permission is also a key point in this correspondence. Original copies of this letter were hand delivered the afternoon of November 1st to William Kreykes, President of Rhode Island Hospital, Vartan Gregorian, President of Brown University, Donald Marsh, Dean of Brown University Medical School and to Steven Brown of the American Civil Liberties Union.

Mr. Brown from the American Civil Liberties Union informed me on November 5th that a meeting would be held on November 8th concerning the study. No other contact had been received by any other parties concerning this issue. I made the decision that the study must be stopped as soon as possible to protect this patient population. At this point, notarized letters of complaint were forwarded to the Rhode Island Attorney General, the Rhode Island Office of the United States Attorney, and the applicable offices

within the Rhode Island Department of Health. (Exhibit F) Additional letters were sent to all the local newspapers, radio stations and television stations. Letters were sent to any advocacy group, public or private, that worked with a chemically dependent constituency. (Exhibit G)

I reported for work on the evening of November 7th and was assigned to the triage area which is away from the constant observation rooms that hold the study patients. Approximately one hour after my shift began, I was requested to report to Elizabeth Powers, R.N to assist her. When I reported, Ms. Powers instructed me to draw blood for the hypoglycemia study from a restrained patient in one of the constant observation rooms. I refused to follow this order explaining that my duties at triage took precedence and also that it would be against my ethical, moral and religious principles to do so. She became angry and told me that, "the patient didn't have the right to refuse," and proceeded to draw the blood for the study herself.

Mrs. Fanning, my supervisor, called me into the office shortly afterward. During this meeting with Mrs. Fanning and Maria Pires, R.N., Associate Director of Adult Patient Services, I was instructed that, "You must follow department standard and draw blood from this patient population and that you must also participate in the ALCO study," a less invasive study about alcohol use that did not provide the patient with informed consent. I again refused citing the lack of informed consent and my opposition to participate based on my ethical, moral and religious principles. At this point, Mrs. Fanning told me that I was being suspended for insubordination for not following department standards and to report to Mary Salisbury, R.N the emergency department Clinical Manager or to Linda St. Angelo, R.N. the Director of Emergency Nursing on Monday morning, November 8th. I interpreted this action as the first step in the hospital's discharge process. According to the Rhode Island

Hospital Employee Handbook (1991), "All suspensions and discharges shall be placed in writing and reviewed by the Director of Employee Relations/designee for consistency and proper documentation. If this review cannot be conducted in advance, the Department Head should suspend the employee pending review." I spoke to Mrs. St. Angelo by phone on November 8th, and she asked for another day to meet with the hospital administration to review the incident. On November 10th, I once again contacted Mrs. St. Angelo. She informed me at this time that the suspension was being changed to a paid suspension until the review was complete.

Later in the day on November 10th, I was contacted by the Providence Phoenix and the Providence Journal about the hypoglycemia study. Pressure by the newspaper coverage (Fish & Prevost, 1993 and Freyer, 1993) and the American Civil Liberties Union forced the hospital to review the original decision of the Institutional Review Board. I was reinstated with back pay and the study was suspended pending review on November 12, 1993.

The researchers maintain, that the objective of the study was to determine if an alcoholic patient becomes hypoglycemic after drinking. (Exhibit A) Dr. Sucov claims there has been no other research in this area except for a different alcoholic/hypoglycemia study conducted by Rhode Island Hospital last year. (Freyer, 1993) This study did not find a link between hypoglycemia and alcohol use. I feel the hidden agenda in this study is the "publish or perish" syndrome that is affecting emergency room doctors nationally. Attending physicians are hired with joint appointments in teaching hospitals. This means that they teach in the local medical school and also perform their duties as a physician within the hospital. Colleges and Universities require that their professors must be published to advance within their profession. This process has carried over to emergency room doctors. Copious amounts of

research are being conducted with no interest whatsoever in the results, or in how the results are obtained. (Kim & Spivey, 1994) I feel that the doctors involved in this study found any easy way to satisfy their research obligation without "getting their hands dirty."

The hospital states in published reports (Fish & Prevost, 1993 and Freyer, 1993) that only ten patients were subjected to blood tests in the twelve days the study ran prior to its suspension. However, if the projected number of three hundred patients to be studied in three months, as stated in Dr. Sucov's memo, is true, (Exhibit A) the actual number of patients in the study would be thirty nine. It is my opinion that the real total is somewhere in between.

Nurses and technicians were told in small meetings, that "the patient can not refuse to participate in this study." A posted written protocol stated, "Patients can not refuse to be part of this study, as they are technically not capable of refusing potentially life-saving care while intoxicated." (Exhibit C) Most staff members took the submissive role of servant to the patriarchal doctor, and followed orders. A few quietly overlooked the study but did not try to influence a change.

Patients were not told, before participation or after discharge, that they had been a research subject. According to Kenneth Arnold, chief legal counsel of Rhode Island Hospital, and Donald Marsh, Dean of Brown University Medical School, the Institutional Review Board gave the researchers permission to waive the informed consent requirement. (Fish & Prevost, 1993 and Freyer, 1993) An Associated Press article in the New York Times (1994) attributes to Mr. Arnold, that Rhode Island Hospital has not written its own ethics guidelines to date. My attempts to contact the Institutional Review Board were unsuccessful because the hospital refused to identify the members.

The physical problems involved with drawing blood from

a sober, cooperative patient are minimal. This is not the case when the patient is intoxicated and refusing the procedure. Drawing blood in these circumstances is dangerous for the patient and staff members. A needle used in these circumstances is potentially a lethal weapon with the high incidence of AIDs in the substance abusing population. Patients are often restrained as described above which creates the high potential for physical and psychological injury. Ernest Winsor of the Massachusetts Law Reform Institute claims that this may even be considered "assault and battery" on the patient. He also believes that, "there's a tendency for people with power and authority to take advantage of poor people."(Fish & Prevost, 1993)

Don Williams, associate director of the Rhode Island Health Department's Division of Health Services Regulation states, "the study probably violated state laws protecting patients." (Fish, 1994) In a conversation with a Health Department senior investigator, I was told that, "the doctors probably would not be punished because they were only following orders." This prophecy proved to be true. It also made my hair stand on end and angered and distressed me. Nazi doctors at the Nuremberg Trials claimed to be only following orders. Most were admonished for following illegal orders and were severely punished. (Shirer, 1960) I guess it is permissible to break the law in Rhode Island if you are a doctor acting under orders.

According to Larry Gastin, executive director of the American Society of Law and Medicine, it would be very rare for researchers to ignore informed consent. (Fish & Prevost, 1993) He obviously has not examined the Rhode Island Hospital Institutional Review Board's record. Ignoring informed consent regulations seems to be the rule rather than the rare exception here. Multiple examples that I am aware of are presented below. The Institutional Review Board

seems to be a rubber stamp for the hospital researchers. There are sixteen members of Rhode Island Hospital's Board, fourteen hospital employees, an attorney affiliated with the hospital's law firm and a pediatric psychiatrist with admitting privileges to the hospital. (Fish, 1994)

There are other research studies that have been conducted without informed consent at Rhode Island Hospital. A similar alcoholic/hypoglycemia study was performed on approximately 300 patients in 1992. This study used the blood drawn for an alcohol level. The results showed that less than one percent of the study patients were hypoglycemic. (Freyer, 1993) At no time was the patient told that their blood was being used for research. Patients who refused to give blood were tied to the stretcher as described above. The results of this research study did not justify the alcoholic/hypoglycemia study that was started last November.

Brown University and Rhode Island Hospital conducted a research study in 1992 using the ALCO-Screen dipstick. All adult patients admitted to the Emergency Department with injuries sustained in an accident of any kind were studied for about six months. Seven thousand to ten thousand patients had this dipstick placed in their mouth to measure alcohol use. Results were entered prominently on the cover sheet of the patient's chart and permanent record. This is a violation of patient confidentiality laws. (cite law) Informed consent was not discussed with any study patients, before, during or after their participation. The study patients were unaware of participation in a study and also were unaware of the chart entry about the study results. Amato DeLuca, president of the Rhode Island Trial Lawyers Association, fears that the notation on a patients chart may place them at legal risk. Mr. DeLuca also calls this procedure "an invasion of privacy." (Fish, 1994) A controlled study using saliva dip sticks was conducted in

Houston in 1991. The results of the study suggest that the saliva test would not be very useful as a screening tool because of its poor predictive value in a population that was not primarily composed of chemically dependent people. (Pate, Hamilton, Park & Strobel, 1993)

The ALCO-Screen dipstick study was reintroduced and expanded in 1993, with ten thousand to twelve thousand research subjects. Children from twelve to eighteen, along with the adult population, were included in this study. Once again, informed consent was omitted, even when a parent was present with their child. The study now only wanted, positive for alcohol use, or negative for alcohol use, noted on the cover sheet of the patient's chart. In a letter to William Kreykes, president of Rhode Island Hospital, I asked that this study be stopped because of a lack of informed consent. (Exhibit H) He responded in writing to me, promising that Kenneth Arnold, chief legal counsel for the hospital, would review every study presently being done. (Exhibit I) This study was not stopped until I made another complaint with the American Civil Liberties Union in January. (Exhibit J) Published reports on this incident quoted Steve Berkey, the president of Chematics, manufacturer of the dipsticks. Mr. Berkey said that he "would be very surprised if the hospital was using the results for research purposes." (Fish, 1994)

One of the most appalling cases of research for the sake of research is an asthma study conducted with children by Dr. Robert Wright of Rhode Island Hospital. I discovered this study when I saw a notice posted on a public bulletin board in the Hasbro Pediatric Hospital's emergency department. (Exhibit K) This study is designed to measure descriptive assessment language used by doctors, of children suffering from an asthma attack. The method used, is for one physician to examine the child and document assessment findings. Then a second doctor repeats the examination and

documents the assessment. The descriptive verbiage is compared later. During the two examinations, which can take up to thirty minutes or more, the standard nebulizer treatment is withheld from the child. Informed consent requires a researcher to inform the patient, or parent, of possible dangers of participating in a research study. A child suffering from an asthma attack can quickly deteriorate and go into respiratory arrest, and die. Was this explained to the parent? Would any parent consent if told the true dangers of participation? I don't think so. Other physicians and nurses not associated with the hospital told me that the assessment verbiage in this case is almost useless. They universally said, "the child either needs a neb or doesn't need a neb." I aggressively attacked this study, because of the inherent danger of death. Sandra Stamoulis, Vice President of Patient Services and Linda St. Angelo, Director of Emergency Nursing met with me at 11:00 P.M. on Friday, March 18th. They both maintained that the study met informed consent regulations and refused to stop the study. I was forced to go public with my complaints once again.

The attitude of Dr. Wright and of Rhode Island Hospital can be described with a quote from the study letter posted on a public bulletin board within this inner city hospital. (Exhibit K) "I have a small daughter who depends on me to put food on the table. If I don't finish this study my wife will probably leave me, and I'll wind up penniless, drunk and smelly in South Providence. So please, please, please, remember to grab the asthma doc before starting a neb."

The "Timi 9" research study is being conducted in one hundred and fifty hospitals in the country. This Ciba-Geigy sponsored study, of hurudin versus hoparin, enrolls individuals who are in the midst of a heart attack. The form used for agreement to participate in the clinical investigation is impeccable. It includes the nature and

remarks made about me by hospital managers in public. The working atmosphere has been extremely difficult and is a contributing factor to my cardiac problems. The longterm damage to my new career may be permanent in Rhode Island. Many nursing leaders have expressed concern about my professional future as a new graduate nurse. Hospital hiring authorities look at me as a "trouble maker." Has my professional career ended before it starts? This fear is always with me. I didn't look for a fight, I just acted as a patient advocate in my role as a future professional nurse. Hopefully, nursing leaders will stand behind me in my search for a career position in nursing.

As I stated above, research on human subjects plays an integral part in conquering new frontiers in health care. All federal agencies should make a thorough review of current statutes and regulations involving human subject experimentation. A joint committee of agency members, should write new uniform regulations that apply to all human subject researchers. These regulations must remove ambiguous language so an institutional review board can properly carry out their mission. Additionally, I believe that an ethics review board on human subject experimentation should be formed to audit the actions of institutional review boards and to respond to complaints. This ethics review board must be given the power to penalize illegal or unethical activities by researchers. The penalties could be the loss of federal funding for the researcher and the institution. The threat of losing federal funding caused the National Institute of Health to institute regulations to protect human subjects in the early 1970s. (Rothman, 1994) This same threat would force institutional review boards to be more vigilant.

As discussions take place about change in emergency room informed consent regulations, abuses are still taking place. I therefore wish to make a formal complaint about

purpose of the project, an explanation of procedures, the discomforts and risks, the benefits, alternative therapies and withdrawal information. However, the reality of the informed consent process is quite different. I have witnessed doctors asking patients, suffering from an excruciatingly painful heart attack, the following question to obtain consent. "Will you agree to let us use the study protocol?" There is no explanation of risks versus benefits or any other required information presented. The patient in this type of pain would probably consent to being murdered if it would take the pain away. I recently spoke to the daughter of a patient who was recruited for this study using the above technique. She reported to me that the family was given no information or choice about using the study medication. It took her close to an hour to stop crying.

Rhode Island Hospital is the second largest employer in the state with powerful connections everywhere. The hospital's board of trustees is composed of many business leaders throughout the community. At least two members also serve on the board of directors of The Providence Journal. A reporter for the newspaper told me that, he has been ordered to "soften" critical articles about Rhode Island Hospital. He also noted times that, the newspaper would not even cover news worthy stories because it would offend Rhode Island Hospital.

The recent consequences of my "whistleblowing" have been an unsuccessful attempt by Rhode Island Hospital to fire me. I have also developed a problem with cardiac tachycardia that has forced me to take a temporary medical leave of absence from the hospital. Sandy Stamoulis, vice president of patient services, and Linda St. Angelo, director of emergency nursing, asked me, "Why don't you quit if you're so unhappy with the way the hospital does things?" Many hospital employees have told me about disparaging

CARDIOLOGIC

TESTIMONY OF

Jeffrey Koepsell, President and CEO

CardioLogic Systems, Inc.

Before the House Committee on Small Business

Subcommittee on Regulation, Business Opportunities and Technology

Monday, May 23, 1994

FOR IMMEDIATE RELEASE
May 23, 1994

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TESTIMONY OF
Jeffrey Koepsell, President and CEO
CardioLogic Systems, Inc.
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Monday, May 23, 1994

Thank you Mr. Chairman. My name is Jeff Koepsell. I am President and CEO of CardioLogic Systems, Inc. (CSI), a Baltimore-based small business. I am here to discuss an issue of great importance to my company and to the field of emergency medicine -- waiver of informed consent in resuscitative research. Pursuant to your request, I will first describe my company and our technology, Vest-CPR. I will then discuss the importance for CSI that U.S. regulatory agencies have the authority and flexibility to grant waivers to the requirement of informed consent for resuscitative research under appropriate circumstances. Using CSI as an example, I will then propose factors that should be considered by regulators in making such a decision. Finally, I will outline the regulatory process and costs we must endure to get our product FDA approved.

CardioLogic Systems, Inc.

Like many other start-up companies in the area of medical device technology, CSI has few employees, no approved products, lots of bills and several anxious investors. Most of the investment in CSI is venture capital. Prior to taking over at CSI, I ran other small medical technology companies and I have much experience with government regulatory agencies. Let me make it clear from the outset that any company I run prides itself in playing by the rules no matter how laborious or expensive the obstacles may be. We believe in our technology and we are working hard to effectively communicate with regulators to get it approved.

In December of 1992, CSI signed a licensing agreement with The Johns Hopkins University (JHU) to further develop a new and innovative Vest-CPR technology originally designed and patented by JHU scientists. CSI will no doubt rise or fall based upon the vest's impact in resuscitative medicine. The CardioLogic Vest-CPR is analogous in appearance to a large blood pressure cuff. Controlled by a computerized pneumatic system which directs compressed air in and out of the vest's bladders, it delivers CPR through an innovative, circumferential pressure approach. The vest system delivers sequential inflation-deflation cycles while maintaining sufficient positive pressure on the chest to

something happened in the interim. A few weeks after we were asked to submit our proposal on informed consent, we were told in no uncertain terms that we must proceed with full prospective informed consent only.

With no other options except to take the technology overseas (FDA assured us they would not look favorably on the data from a foreign study) or to halt the project, we modified our protocol to include a plan for prospective informed consent. This is an outrageous expenditure of money and resources for a small business. We have had to offer to pay for staff people at each of the study sites to screen each eligible subject that may qualify for the protocol. If we did not offer to do this, the hospitals clearly would not agree to participate in the study. Our projections indicate that we will have to prescreen up to 260,000 patients to obtain the 400 eligible patients we need for the study. By following this protocol, we will involve and potentially worry hundreds of thousands of patients needlessly and the cost to CSI may exceed $1,400,000. There is no telling how long this process may delay patient accrual. The Small Business Committee should be particularly sensitive to a policy which forces us to spend $1.4 million to get informed consent on a trial intending to enroll 400 patients.

Already, one hospital has decided that the type of informed consent required by FDA will be too much of a burden on their patients and staff despite our offer to hire staff members. The Chief Investigator wrote that "[E]ven though CardioLogic would be willing to provide assistance in obtaining informed consent from these patients, it was felt that they would have significant anxiety and subsequent questions for their continuing care physicians." One of his nurse managers said "we would scare to death" 300 patients who would not arrest each month.

I must emphasize that our company places the autonomy, safety and well being of patients above all else. It is our firm belief that patients in cardiac arrest have a significantly better chance of survival with the vest system than they do with standard CPR and we are anxious to confirm the preliminary studies. Several IRB's made independent decisions that a waiver of prospective informed consent was appropriate to test the CPR system in their hospitals. Unfortunately, FDA's regulations, strictly interpreted, do not allow them to make the same judgement. In the past, there have been studies where FDA has allowed a "deferred consent" approach in circumstances where the risk/benefit

from each patient that may qualify for our protocol that is admitted to a hospital study site.

Because 70% of cardiac arrests occur outside the hospital setting, we are developing a portable model of the Vest-CPR for the "first responder" market. FDA will require more studies for that use, even if they have an approval for the hospital setting and scientific data shows that Vest-CPR is more effective and as safe as manual CPR. The agency told us recently that prospective informed consent will again be required for additional trials in the first responder market, even though they are aware that obtaining such consent in these emergencies is a virtual impossibility. Herein lies our informed consent dilemma.

Waiver of Informed Consent In Resuscitative Research Trials

Mr. Chairman, you asked that I comment on how these government policies in interpreting the proper application of a waiver of informed consent have affected and will continue to affect my small business. The short answer is that government policies have fostered our creation, but now threaten our future. It was FDA's earlier policy, allowing a waiver of informed consent, that allowed JHU to prove the vest technology had great promise. Today, perhaps because of isolated abuses by others and media focus on problems from decades ago, CSI is faced with a new rigid government policy on informed consent in resuscitative research. If that policy is not made more flexible for life saving resuscitative research where prospective informed consent cannot reasonably be obtained, like the "first responder" market, CSI will likely go bankrupt. More importantly, medical progress in emergency medicine in the United States will stop and lives will needlessly be lost.

It is quite simple – for our technology to survive the business must be profitable. To make money, we must get our product approved and sell it in a market. The true market for the vest system – and the place where it can save the most lives – is in the ambulatory care first responder market.

and a requirement that the study provide valuable evidence on the differences between experimental and standard therapies for the future.

Miller's conditions for the justifiability of resuscitation research without informed consent are:

a) patient is comatose;

b) lifesaving treatment must be given immediately;

c) given all available evidence, there is reason to believe that the probability of death or severe deficit with experimental or control therapy is not greater than the probability of death or severe deficit on usual therapy;

d) given all available evidence, there is reason to believe that the probability of normal or near-normal outcome is greater on experimental or control therapy than on usual therapy; and

e) the study can provide evidence on whether there is a significant difference between experimental and control therapies in the incidence of normal or near normal survival.

(Critical Care Medicine, October, 1988; 16:1059)

CSI's Vest-CPR system is an ideal candidate to be considered for such an exception to informed consent based upon the above criteria. It is our hope that FDA and other governmental regulatory bodies will soon be able to make informed consent decisions unhampered by inadequate regulations. FDA should be able to weigh benefits and risks and consider the unique problems of obtaining informed consent in resuscitation research in the same way as IRB's. The outcome of this hearing and its resultant affect on guidelines for informed consent in resuscitation research is absolutely critical to the ability of my small business to survive and for technical innovation in emergency medicine to improve patient outcome in the future.

of the solid protections built into our systems for human subjects of research. Please do not lose sight of the fact that critical advances in emergency medical research in the past, present and future rely or have relied on exceptions to prospective informed consent. If we had these same impediments to emergency medicine research in the 1950s, we might not have the benefit of such important advances as ventilators and defibrillators for emergency use. There are, and will continue to be, appropriate circumstances to waive prospective informed consent for emergency resuscitative research. If one objective of the subcommittee is to increase business opportunities of small technology businesses by resolving regulatory problems, the case could not be made more clear. Both the FDA and HHS regulations need to be revised to account for resuscitative research trials. I ask you and your colleagues to legislate or to mandate new regulations to allow appropriate emergency research to continue. Thank you.

Testimony to:
Subcommittee on Regulation, Business Opportunities and Technology,
United States House of Representatives

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215-349-8600

May 23, 1994

Let me begin by thanking you Congressman Wyden and the other members of the committee for the opportunity to offer testimony to you on a matter of great importance in the conduct of research. The question of how to conduct research in dire or emergency situations involving human subjects who are not, for various reasons, competent to give their consent is one of the most difficult facing those concerned about the ethics of human experimentation. Unfortunately, the problems raised by research under these most difficult circumstances have not received the attention required from scholars, regulatory agencies and public policy makers. It is commendable that your subcommittee has chosen to inquire into the various ethical, legal and policy issues raised by such research.

I know first hand how vexing the questions raised by research under emergency circumstances can be. Before accepting a new position as the Director for the Center of Bioethics at the University of Pennsylvania, I worked for seven years as the Director of the Center for Biomedical Ethics at the University of Minnesota. While there I had the opportunity to learn about the ethical issues raised by a study investigating a device intended to be used to help resuscitate persons suddenly stricken with heart failure.

The device, a lightweight plunger known as the Ambu CardioPump, made by a Danish company, Ambu International, provides more active compression and decompression force than existing CPR techniques. In a recently published study in the Journal of the American Medical Association (May 11, 1994), a research team led by Dr. Keith Lurie from the University of Minnesota reported higher rates of success in the return of heart function for some subjects than were achieved with standard CPR techniques.

This paper was accompanied by and editorial written by a contributing editor to the Journal of the American Medical Association which reported that, despite the fact that the study had been approved by the Institutional Review Board of St. Paul Ramsey Hospital in St. Paul, Minnesota, it was terminated by the FDA before the researchers had collected all of the data they had intended to collect. The FDA decided not to permit the enrollment of all of the subjects that had been called for in the study design because of concerns about the inability to obtain informed consent from those upon whom the Ambu Pump was being tested. Indeed, while there policies differ, both the FDA and the NIH prohibit most forms of research where the full informed consent of the subject cannot be

obtained. Under certain circumstances the FDA will permit research under dire or emergency circumstances while the NIH has made it clear that it does not approve of research done informed consent obtained after the fact from subjects.

In the discussion that has followed in the wake of the publication of the Ambu Pump report many people expressed outrage that a beneficial device was being withheld from those suffering life-threatening cardiac arrest. But, this is not an accurate description of the current state of affairs with respect to this new technique for CPR.

The researchers themselves reported limited success in restoring circulation in a very small sample of those whose hearts had stopped--those for whom it was know that cardiac arrest had taken place for less than ten minutes before CPR was tried. It is important to note that there is no evidence that people who had the device administered actually remained alive longer or once they received treatment at a hospital then did those who had the now available methods of CPR given to them. And it is important to note that hardly anyone would find it useful or beneficial to use a device which carries a much higher risk of restoring cardiac function then it does restoring neurological function.

The Ambu CardioPump study raises a host of tough moral questions. Who, if anyone, should be asked to consent to the testing of the device? Would there be any circumstances under which it would be morally right to halt a study such as this and who ought make such a decision? What sorts of consent to undertake this study are needed from city officials, emergency room personnel and the fire department and health care providers responding to emergency situations? The answers to these questions are made somewhat more complex by the fact that the financial stakes involved in the case of the Ambu CardioPump were the device shown to work are significant.

CPR research raises many questions about what to do when the traditional protections of subject autonomy, informed consent and review by human experimentation committees or institutional review boards (IRBs) are reduced to only committee review by the incapacity of the subject to provide or withhold consent. It is important to note that there are many other situations in which the

need to undertake important research arises in situations where patient competency to consent is suspect or absent.

These range from cases in which a parent suddenly discovers that his child faces immediate death unless a lobe of lung is donated and feel that the pressure of time and family duty permit no choice, to emergency first use of new artificial organs and synthetic fluids such as blood and blood pressure stabilizers following sudden, unexpected acute trauma, to innovative methods for helping someone survive acute renal failure or a massive stroke.

Questions about the morality of research in dire circumstances for persons unable to consent are not confined to physical emergencies. Research intended to permit better management of an acute psychotic episode or sudden violent outburst related to drug use pose similar moral questions about when research ought be done, with whose approval and with what sort of supervision.

One way to begin to articulate a public policy response to the many moral problems involved in research under emergency circumstances is to try and distinguish the kinds of subjects who may be potential candidates for research under dire or emergency settings. I think the following groups, while perhaps not exhaustive, are representative of those especially vulnerable persons likely to be the subjects of research under emergency circumstances;

1. Competent persons facing emergencies or unanticipated crises.

   In this group are people who are otherwise competent but who are rendered questionably competent by the nature of a sudden accident or the unanticipated onset of disease. The very occurrence of a severe, painful or debilitating disorder may render someone psychologically unable to give true informed consent. Also if the stakes are especially high, if the situation is one of life or death, a person may feel so coerced by the circumstances that they face that they are unable or unwilling to make choices.

2. Persons who were competent but who are rendered suddenly incompetent by an acute accident or disease.

In this group are people who are suddenly rendered manifestly incompetent by a sudden devastating health crisis such as a massive heart attack, stroke, psychotic episode or traumatic accident. They are not conscious or, if they are, are unable to communicate. Those in such circumstances are obviously unable to give consent to any form of research or experiment.

3. Persons who were never competent and who face a sudden or emergency disease or accident situations.

In this group are children, the severely retarded and some persons who are mentally ill. They have never had the capacity to give consent and are unable to do so for themselves in an emergency or unanticipated crisis.

Each of the persons in these general categories may or may not have a proxy decision-maker available. This person may or may not be a family member. And the proxy may or may not have been formally designated as such by the person facing the need to make a decision about research under emergency circumstances.

What is obvious from these facts about the range of persons involved in the testing of new or innovative procedures, drugs or devices is that the doctrine of informed consent, which has been at the heart of American research ethics since the days of the Nuremberg trials, will not function for many members of these groups under dire, acute or emergency circumstances. Many scientists, ethicists and physicians have struggled to preserve the doctrine by introducing concepts such as "deferred consent" or "presumed consent". The latter idea is a version of what is sometimes called the "therapeutic waiver" whereby in an emergency the treatment of life threatening conditions is allowed and expected both legally and ethically.

But, it seems obvious that deferred consent and related notions will not suffice to bolster informed consent to research under dire and acute emergency circumstances. Obtaining an after the fact consent to research may be helpful in terms of informing subjects as to what was done to them but a ratification after the fact is not the same as a consent. And for some persons after the fact consent is meaningless since they may lack the capacity to provide it either as a result of the trauma or because their capacity was impaired to begin with.

My position on research in acute, emergency and unanticipated dire circumstances is that such research is important. Americans expect that medicine will pursue better methods for dealing with sudden heart attacks, allergic reactions, acute overdoses, toxic exposures, traumatic injuries and psychotic episodes. Research on these terrible problems must and should be encouraged. However, while I by no means favor prohibiting or banning such research, I believe that our society in general and those charged with the regulation of research in particular must pay much more careful attention the ethics and regulations governing this type of research.

It should be a given in any research context that informed consent must be pursued. The failure to obtain consent is a burden that must always be born by those doing research. Prospective subjects should not be presumed incapable of giving consent simply due to the nature of their acute medical problems. But, it must also be recognized that many of the potential subjects involved in emergencies are facing such dire and difficult circumstances that there ability to give consent is severely compromised if not completely absent.

Since informed consent cannot function for some individuals in acute and emergency research then the obvious place to turn in order to maintain the protection of subject interests and dignity is to the process of peer review. Specifically, institutional review boards or IRBs must bear a very heavy load of responsibility where acute or emergency research is concerned. For, they are the persons who must decide whether such research is morally justified.

The criteria for reviewing and approving emergency research by an IRB are, at present, inadequate. No special regulations specific to the circumstances exist to guide IRBs in their deliberations. I would suggest that this situation must be changed.

The burden of assuring the ethical conduct of research in dire, emergency situations where consent is not possible should be placed squarely on the shoulders of IRBs. Regulations are needed which specify criteria for IRBs to consider with respect to; subject selection, disclosure of conflicts of interest, prior animal, laboratory and clinical research, the competency of investigators, acceptable levels of risk, the goals of research in acute and emergency circumstances, the systematic review of research outcomes and the ongoing debriefing of a subset of subjects and their proxies. Let me outline some of the

specific areas where more regulation and guidance for IRBs seems warranted;

Subject selection: In undertaking research on acute or emergency circumstances there is currently little guidance available as to which groups or individuals ought be recruited. For example, should only persons with proxy decision-makers of some sort be approached? Is research on children every justified and which children? Should the size of the subject pool to be studied be varied according to the severity of the disease or ailment to be examined. Should prior research at the bench or with animals be done to a greater extent when the subject under investigation will lead to use under emergency or dire circumstances?

It should be made clear that whenever a drug, device or technique can be tested on a population with a condition or problem similar or analogous to that which arises in an emergency where informed consent is possible, research should be done on this group first. For example, in the case of the testing of new devices for CPR it would be important to test the device on persons who might be expected to undergo cardiac arrest in hospitals, hospices or nursing homes who might consent to serve as subjects for its use before testing the device in the field.

Conflict of interest. Should those who conduct research under circumstances in which informed consent is imperiled or impossible divest themselves of any potential for personal profit or financial gain. Is it not the case that when subjects cannot really give their consent that researchers must strive to minimize any suggestion that they are taking advantage of or exploiting vulnerable subjects by not only disclosing conflicts of interest but also removing them prior to conducting investigations.

Acceptable levels of risk. Should any research be permitted when the risks involved are more than minimal as is now the case when research on children is conducted. Should all research in emergency circumstances be undertaken with therapeutic intent for the subjects involved? Should IRBs considering research on vulnerable subjects in dire circumstances add members for these deliberations who have some experience with the disease or ailment which is to be the subject of research. And can research every legitimately be conducted if researchers are not in a position of equipoise between available treatments and new ones. That is unless researchers

believe that the new intervention is at least as helpful as existing interventions for the treatment of diseases, injuries or ailments they ought not be allowed to proceed.

Endpoints of research. It would seem as if any study on vulnerable subjects in dire circumstances should include in its design mandatory and timely review by an independent body of all research results so as to permit the termination of the study if it appears as if it causing harm to subjects. The standards of acceptable risk ought not be the same when the informed consent of those participating cannot be obtained or is not reliable. Those conducting research on vulnerable subjects have an obligation to assure that the study is not conducted longer than is necessary to obtain valid findings and that what constitutes validity is subject to input from an IRB appropriately constituted to bring to bear lay as well as objective professional opinion.

In addition to more specific regulatory mandates, IRBs need to be given the resources to cope with these additional oversight and monitoring burdens. In addition to clear guidance they need some fiscal support to permit them to take the time that monitoring research conducted in dire or emergency circumstances requires. Where special populations are involved it may be necessary to move from local to regional or even national review. And when informed consent is impossible then the FDA and OPRR at the NIH should insist upon mandatory unannounced audits of the records of such studies.

We cannot let the struggle to find better ways to cope unexpected emergencies and the sudden onset of ill health fall victim to moral priggishness when it comes to the ethics of research. But, neither should we treat those who are rendered unable to consent by injury, disease or circumstances as if they were objects rather than persons. The best we can due is to subject proposals for research in these instances to rigorous review and oversight. To do their best we need to give those charged with providing the review function more specific guidelines as to what to look for and the resources to adequately carry out their vital roles.

TESTIMONY BEFORE SUBCOMMITTEE ON REGULATION,
BUSINESS OPPORTUNITIES AND TECHNOLOGY
Ron Wyden, Chairman (23 May 1994)

Jay Katz

In reading your letter of invitation to testify before your Subcommittee on the regulation of human experimentation, I was struck by the emphasis you have placed on "consent" and the protection of the "basic human rights" of research subjects, as well as your concerns about "the effectiveness of government agencies, institutional review boards, sponsors of new drugs and devices, and individual medical investigators" in regulating the human experimentation process. These are indeed fundamental issues that require sustained thought. I cannot, of course, address all the questions concerning these issues that you have posed to me and I shall submit an article "Human Experimentation and Human Rights", recently published in the Saint Louis University Law Review which speaks at greater length to many of your concerns. In that article I did not, as I shall not this morning, comment on specific remedies because, as I shall soon explain, piecemeal approaches to these large and complex issues will not work now any better than they have in the past.

Let me respond first, albeit all too briefly, to your questions on the history of informed consent, the evolution of government regulations of protecting human subjects, and the current status of these protections. Before doing so, you need to appreciate that human research in medicine is a recent development. While the beginning of human research dates back to the late 19th century, it was not until 50 years ago, subsequent to World War II, that human research increased in magnitude on a scale unprecedented in medical history. Indeed, in today's world medical practice often encompasses both therapeutic and experimental aspects.

The radical transformation of medical practice which has led to an increasing number of patients being used as subjects of research for the sake of medical science, however, has not been accompanied by thoroughgoing reappraisal of physicians' ethical obligations in a post-Hippocratic age. Instead, physician-investigators continue to obfuscate the distinction between research and therapy, and in turn, between patients and subjects. Investigators do not sufficiently appreciate that in clinical research patients are used as means for the ends of science while in therapeutic encounters physicians are expected to attend solely to the welfare of individual patients. Thus, physician-investigators, socialized in their medical training to become doctors to their patients, are prone to extend the societal mandate to care for the sick, and do so with considerable discretion (a mandate which was delegated to doctors at the turn of this century by legislative enactments), to a mandate to use patients for purposes of research in order to advance the frontiers of knowledge.

The common law doctrine of informed consent was in part a response to medicine's spectacular advances in medical technology which could confer great benefits and at the same time expose patients to considerable harm. It sought to impose greater disclosure obligations on physicians in order to escape legal liability for not having sufficiently informed patients about risks, benefits and alternatives inherent in any treatment options. The doctrine was first promulgated in a 1957 California opinion and then construed in greater detail in a 1960 Kansas and then in a 1972 D.C. Court of Appeals decision. All three decisions were handed down in response to judges' dawning awareness that the wide discretion which physicians had enjoyed in clinical practice to withhold information from patients and to make unilateral decisions on behalf of patients needed to be curtailed. The doctrine of informed consent, however, inadequately protects patients'

decisional authority over their medical fate. I have explored this problem at length in my book The Silent World of Doctor and Patient and in subsequent articles. But, in passing, I need to draw your attention to the fact that the inadequacies of the consent process in clinical practice have cast a dark shadow over the consent process in clinical research.

To turn now to the research setting: Ever since the mid-19th century, medical investigators have, though only on rare occasions, noted that patient-subjects's consent should be obtained. They never clarified, however, what they meant by consent. Most likely they only envisioned that patients should be informed about the research dimension of the intervention and then acquiesce to doctors' orders. With one exception, it was not until 1947, in the wake of medical experiments conducted in concentration camps by Nazi physicians, that consent was enshrined as a basic requirement for the conduct of research. In its Nuremberg Code, the Allied Military Tribunal established as a first and most uncompromising principle that "the voluntary consent of the human subjects of research is absolutely essential." The Nuremberg Code to be sure required modifications but, in my view, its first principle did not except for research with incompetent patient-subjects. What happened instead was that the first principle was eventually weakened by the felt need to balance the interests of patient-subject to inviolability of person and body against the interests of science and society to acquire knowledge for the benefit of mankind. These tensions inherent in human research have to this day not been satisfactorily resolved.

The scientific community only paid lip service to consent, and research practices did not change significantly during the subsequent 25 years. When in 1972 the Tuskegee Syphilis Study - conducted since 1932 (that is before, during and for 25 years after the revelations of Nuremberg) by the U.S. Public Health in Macon County, Alabama with 400 poor

uneducated African Americans - came to public attention, many of the investigators and their defenders claimed that informed consent was during these years not a basic requirement.

I was a member of the DHEW Tuskegee Syphilis Study Hoc Advisory Committee which recommended in 1972 that the Study be terminated forthwith. I listened then to all the justifications advanced for an experiment that deserved moral and legal condemnation. I now serve on the President's Advisory Committee on Human Radiation Experiments and am beginning to learn again about similar justifications for experiments conducted during the 1940's to early 1970's. (I must interrupt here and draw your attention to an egregious error in the Subcommittee Staff's report on "Human Guinea Pigs." On page 6 it states that "[n]o disclosure was made that [the African American males] would be infected with syphilis." This is not true. All the subjects had contracted syphilis prior to their participation in the Study. They were then deceived by the USPHS physicians and kept from receiving treatment, most notably after penicillin proved to be a simple and effective therapy. This was terrible and inexcusable but the investigators did not do worse by infecting them with syphilis. It is important that you correct this error because the belief is widespread within the African American community that their (and our) brethren were deliberately infected with syphilis and that therefore researchers similarly are now infecting African Americans subjects with AIDS. It would truly be a pity if such mistaken notions were to keep patients from seeking treatment).

Ultimately, the Tuskegee Syphilis Study Ad Hoc Advisory Committee also made detailed recommendations on the regulation of human research. Since from the mid-1960's I had taught seminars on the regulation of human research at Yale Law School, and just prior to the revelations of the Tuskegee Syphilis Study published the first comprehensive book on Experimentation with Human Beings, I chaired the subcommittee

charged with formulating new policies for the conduct of research. One of our major recommendations, about which I shall soon say more, was the establishment of a National Human Experimentation Board.

Senator Edward Kennedy held hearings on a Bill which he had drafted with my assistance that incorporated this idea. It never received the support of his colleagues in the Senate. At the hearings on his Bill the Assistant Secretary of HEW argued that such sweeping reforms were not necessary and that HEW would soon propose new regulations that would adequately protect the rights of research subjects. The cornerstones of the new HEW regulations, enacted in 1975, were two: (1) detailed criteria for obtaining informed consent, and (2) the establishment of local institutional review boards (IRBs) which would review and approve research protocols including informed consent forms. The idea of giving supervisory authority to IRBs dates back to the mid-1960's when the USPHS and NIH established such boards to review government sponsored research. In the mid-1970's, subsequent to the Federal Regulations, institutions were also required to provide assurances that all research with human beings would be reviewed by IRBs, whether government-supported or not.

In the final report of the Tuskegee Syphilis Study Ad Hoc Advisory Committee, we urged that a National Human Experimentation Board be established and I continue to believe that such a Board is needed. We then recommended that

> 1. Congress should establish a permanent body with the authority to regulate <u>at least</u> all Federally supported research involving human subjects, whether it is conducted in intramural or extramural settings, or sponsored by DHEW or other government agencies, such as the Department of Defense. Ideally, the authority of this body should extend to all research activities, even those not Federally supported. But such a proposal may raise major jurisdictional problems. This body could be called the National Human Investigation Board. The Board should be independent of DHEW, for we do not believe that the agency which both conducts a great

> deal of research itself and supports much of the research that is carried on elsewhere is in a position to carry out [disinterestedly] the functions we have in mind. The members of the Board should be appointed from diverse professional and scientific disciplines, and should include representatives from the public at large.
>
> 2. The primary responsibility of the National Human Investigation Board should be to formulate research policies, in much greater detail and with much more clarity than is presently the case. The Board must promulgate detailed procedures to govern the implementation of its policies by institutional review committees. It must also promulgate procedures for the review of research decisions and their consequences. In particular, this Board should establish procedures for the publication of important institutional committee and Board decisions. Publication of such decisions would permit their intensive study both inside and outside the medical profession and would be a first step toward the case-by-case development of policies governing human experimentation. We regard such a development, analogous to the experience of the common law, as the best hope for ultimately providing workable standards for the regulation of the human experimentation process.

Your committee's concern about research with "mentally incapacitated persons with unapproved (or approved) drugs and medical devices" illustrates the need for a National Human Experimentation Board. In turning to your concerns, I shall also comment, as you asked me to, on the "deferred consent" standard. First though, let me make a brief comment about your question as to whether "[I] agree" with Arthur Caplan's statement that "informed consent for emergency room situations [is] 'a regulatory swamp' ... [as a result] of the perceived differences and contradictions between the standards variously imposed by (1) individual IRBs, (2) the NIH and (3) the Food and Drug Administration." I agree; yet, his contentions only identify the tip of the iceberg. Even if these "differences and contradictions" were reconciled, we would still be faced with unresolved problems, precisely because informed consent

is largely meaningless when research with mentally incompetent patient-subjects in emergency rooms is in issue. In these situations we must confront a number of questions: (1) how should the tensions between the protection of human subjects to inviolability of person and body, on the one hand, and the advancement of knowledge, on the other be resolved; (2) can in these situations patient-subjects ever be recruited for the sake of science; and (3) if so, who should be invested with the authority to make such awesome decisions?

By now it should be quite clear that I do not believe that local IRBs should be allowed to make such decisions for competent patients which go to the heart of our democratic values of autonomy and self-determination, and for incompetent patients which would allow their use as means for others' ends. I want to offer some additional observations in support of my contentions:

(1) Research with human beings should be carried on with the minimal number of projects (and subjects) necessary to obtain important scientific results. At present IRBs work in isolation from other IRBs and, thus, similar experiments are being carried out at countless institutions that often only duplicate studies already in progress. Using human beings unnecessarily, as if they were as readily available as guinea pigs, is, I believe, unwarranted. A National Human Investigation Board could orchestrate efforts to keep unnecessary repetitions of experiments to a minimum.

(2) The majority of IRB members are on the faculty of the institutions to which the investigators belong. For example, the IRB at Yale-New Haven Medical Center consists of 26 members of whom 15 are full-time medical school faculty, 5 others are affiliated with the Medical Center, and 4 are medical students. The IRB members not only share similar interests and objectives but they also know, when sitting in judgment of a research protocol, that their proposals may soon be subjected to similar scrutiny. Thus, it is unlikely that

members of IRBs will hold investigators to standards that will protect the subjects of research if doing so would place impediments on the conduct of research and affect the well being of their colleagues (and eventually also their own well being) in decisive ways;

(3) The evolution of the idea of "deferred consent" is an example in point. It originated at a midwestern medical center, when its IRB was reviewing a research project on head trauma to which patient-subjects could not consent and members of their families were deemed too distraught to give meaningful consent. Eventually the IRB decided that

> [f]amilies would be informed at the time of admission that their kin would be entered in an experimental project, but would not be explicitly told that they could refuse, or be asked at that time to consent either orally or in writing. Within 48 hours, however, the investigators would have to obtain written consent from the family to continue the patient in the study. ... Initial notification gave an opportunity for withdrawal in those families who might feel especially strongly about the issue.

Such decisions which would essentially compel patients to participate in research without consent and, in addition, could also create guilt feelings in family members for not having listened carefully and then objected to their loved ones' participation in the research, should not be made by local IRBs.

Furthermore, the author of a recent article, published in the Journal of the American Medical Association, has argued that "deferred consent, compassionate use, implied consent, consent at hospital admission, or waiver of consent...have tried to follow the spirit of the regulations, the intent of which is to protect the rights, safety and welfare of human subjects." If she is correct that the words of the regulations grant such license to IRBs, then it is an authority which should not be delegated to them. For, as Tom Beauchamp has cogently observed, deferred consent and, I would

add, all its related forms are best understood as "not obtaining consent at all."

(4) Local IRBs are under pressure, not only from investigators but from their own institutions as well, to approve research protocols. Medical research since World War II has become a research industrial complex. Academic institutions rely on the revenues which accrue from the assessment of indirect costs to the providers of grants. Research proposals have to be generated and completed at a rapid rate to assure future grant support. Thus, investigators are under considerable pressure to recruit subjects as quickly as possible to support the institutions' buildings, laboratories, staff and salaries. With respect to the needs of their institutions, and career advancement and future grant support as well, physician-investigators are thus the victims of an institutional system (their own institutions and the National Institutes of Health) which penalizes them if in fulfillment of their ethical disclosure obligations toward patient-subjects, the pace of research would be slowed. These pressures impact significantly on the speed with which informed consent is obtained and the ways in which the process is conducted so that patient-subjects will not refuse to participate.

There are other examples of inattentiveness to the informed consent process. I understand that you are familiar with the UCLA schizophrenia project which I also discussed in my St. Louis Law Journal article. Thus, I need not say more about it. Let me mention, however, that the Federal Regulations on informed consent are in need of a thoroughgoing reevaluation from many perspectives. This is another task for the National Human Investigation Board. Most generally, the informed consent requirement should emphasize that taking informed consent seriously in research negotiations obligates physician-investigators to spend considerable time with patient-subjects. They should provide explicit instructions

on the lengths to which investigators must go in explaining themselves and their intentions so that patient-subjects will not be misled. Physician-investigators need to be cautioned that the requirement of informed consent for research is much more stringent than it is for therapeutic settings. More specifically, the information to be provided in informed consent forms needs to be thoroughly reevaluated. At present they are often too incomprehensible not only because they are written at a higher reading level than is appropriate for the intended population but also because they include too much distracting technical information of little consequence to the decisions patient-subjects must make. Indeed, at present, subjects are overwhelmed with unnecessary scientific information that clarifies little and serves more the purpose of obscuring crucial information that they need to know.

(5) Increasingly, research is being supported by pharmaceutical companies and biotechnical companies with economic rewards accruing to medical institutions and investigators. The conflict of interest problems which such arrangements spawn are troublesome and they too must be examined in depth and regulated by a National Human Investigation Board.

These problems are now compounded by the proliferation of so-called free-standing IRBs which operate outside university settings. Their activities deserve your attention. From what I have learned so far, they are insufficiently regulated. What concerns me to begin with is that these IRBs are for-profit enterprises and that the owners appoint their ethical review committees who are paid by the owners and serve at their pleasure. In such settings conflict of interest is surely an ever-present danger. Let me provide one example of anecdotal evidence. Last year, I asked the owner of one such IRB, whom I judged to be a thoughtful and caring person, whether she had ever rejected a research proposal. Her answer was an unqualified "No," and she explained further that she

would of course suggest improvements in protocol design but outright rejection was too delicate a matter.

In conclusion, let me emphasize once again that the Board I envision should have the authority to formulate research policies that seek to resolve the inevitable tensions between the inviolability of subjects of research and the claims of science and society to advance knowledge. Such a Board's proposed policies, of course, should first be subjected to a relentless public debate and then also approved by Congress, particularly when, for example, in research with incompetent subjects basic values of our democratic society have to be tampered with for our benefit. Such decisions should not be left to the low visibility and unreviewability of local IRBs. IRBs will still have important functions to perform but their work will be guided by a national Board to whom they will be held accountable and to whom they can also turn for advice.

The importance of research has captured the imagination of the Western World and is now being carried forward on an unprecedented scale and with great expectations of the rewards it can bestow on mankind. Yet, in the quest for progress -- the rewards it can also bestow on individual investigators, medical institutions, and pharmaceutical industries -- the danger is great that deeply held moral values of respect for, and the inviolability of, individual citizen-patient-subjects will be eroded. This may be a price not worth paying. If, as some fear, a National Human Investigation Board will slow the pace of medical advances by forcing society to make difficult moral choices in bright sunlight that could make research more time consuming to conduct, so be it. I am not convinced that this will happen, but if it does, I believe it is a far better option to embrace than our being corrupted by practices in secret. The recent revelations about the radiation experiments are an example in point.

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Office of the Dean

May 18, 1994

The Honorable Ron Wyden
U.S. House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, & Technology
B-363 Rayburn House Office Building
Washington, D.C. 20515-6318

Dear Mr. Wyden:

I am pleased to provide testimony on the IRB process to the investigative hearing being held by the Subcommittee on Regulation, Business Opportunities, and Technology on May 23, 1994. My remarks will represent the opinions of the two institutional review boards (IRB) serving the faculty at The Johns Hopkins University School of Medicine campuses. The two IRBs are the Joint Committee on Clinical Investigation (JCCI), that serves the School of Medicine and The Johns Hopkins Hospital, and the Bayview Medical Center IRB (formerly the Francis Scott Key IRB) that serves the Bayview Medical Center campus. This document and the summary remarks at the hearing echo some of the points made to the Subcommittee in a letter from me and Dr. Thomas Hendrix (Chairman of the JCCI) dated 2/22/94. In response to your letter of 2/29/94, the following comments are offered.

"-- Describe the role or mission of a typical IRB... and its general process for reviewing research proposals."

We believe that the best way to answer this question is by quoting from the letter to the President from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research dated 9/1/78:

> "The Commission's deliberations on Institutional Review Boards began with the premise that investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others who are independent of the research must share this responsibility, because investigators have a potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects of their research. The Commission concluded that to assure protection of the rights of human subjects, proposed research involving them should be reviewed by Institutional Review Boards operating pursuant to federal regulation and located in institutions where the research is to be conducted."

At Johns Hopkins, the members of the IRBs understand their primary role is protecting the rights and welfare of prospective human subjects. This mandate requires serious attention to the research proposals that are submitted. The IRBs give careful consideration to the rights and welfare of subjects, including an assessment of the risk:benefit ratio. The IRBs must determine whether the possible benefit to be derived from conduct of a specific project outweighs possible risks to subjects who would be approached to participate.

An important right of all prospective human subjects is the right to decide whether or not to participate in a research study. The IRBs believe that examination of proposed consent processes and attention to the documentation of the informed consent process via use of a written consent form is essential in determining whether or not a project may be conducted.

Although attendance to the ethics of involving humans in research protocols is the primary role of IRBs, at this institution a secondary, but major role, is that of provision of peer review of clinical investigation in order to ensure that the best science is done in the most ethical way possible. Such peer review of human subjects research projects serves an educational purpose for faculty and trainees who conduct this type of research, as it affords them the opportunity to obtain input and assistance in design, conduct, and analysis of the results from clinical trials.

All IRBs must abide by the federal regulations for the conduct of human subjects research published by DHHS and FDA. In addition, the three guiding principles of the Belmont Report of respect for persons, beneficence, and justice must be applied in an IRB's review of proposed human subjects research. We cannot speak knowledgeably about variation of the IRB review process as practiced by individual institutions. Review procedures, committee size, and administrative support provided to run an IRB are dependent upon the number of projects conducted at an institution, the funding sources for the research activity, and the perceived impact of clinical research upon an institution. Therefore, what constitutes an adequate review process for a community institution may not necessarily be the same review process that would apply to large tertiary care centers, such as Hopkins.

Federal regulations mandate the minimum composition for IRBs. These regulations require that individuals who are unaffiliated with the Institution conducting the research and who are not scientists must be part of the IRB. The JCCI currently has 23 members and the JHBMC IRB has 18 members. We believe that inclusion of members from a wide variety of backgrounds promotes a broad, critical review process.

The regulatory requirement to include unaffiliated members (so called lay members) optimizes the chance that other non-medical people will understand the research proposed. If a physician can explain to the unaffiliated, non-medical members what the science is about, it increases the chances that the population to be approached to join the study would also understand the explanation. The role of unaffiliated members in the human subjects research review process assures a greater level of attention to consent issues than is given to consent processes involving standard medical practice and procedures.

The review process for the two IRBs serving the School of Medicine campuses is identical in terms of application requirements, review process by the IRB, and consent requirements. Attachment A is a copy of the application packet for submission of a new human subjects research protocol. The application is known as an RPN form. When the RPN application is received, a copy of the RPN is distributed to each member of the IRB for review and comment.

The IRBs use an Executive Subcommittee system to assemble the comments from all members into a written communication to the principal investigator of a project. The members of the Executive Subcommittee are also members of the full IRB. These two Subcommittees meet each week to review applications from their respective campuses. They formulate the agenda for full board meetings and review questions/comments/correspondence that is generated regarding applications.

The full boards meet twice each month. Investigators are invited to attend convened meetings when the proposed project concerns issues which require intensive discussion. It is not unusual for the boards to meet with an investigator more than once when difficult protocol questions are raised. It is only at the convened full Board meetings that final actions on RPNs are taken. Further details of our system for reviewing proposals may be obtained in the guidelines booklets issued by each board. Copies will be made available to the Subcommittee at its request.

"Describe the problems faced by IRB in conducting their reviews. For example, how is research conducted in the emergency room different from research conducted in other areas of the hospital? What are the obstacles faced by IRBs and by medical researchers, particularly with emergency room trials, in securing appropriate informed consent from human subjects?"

The use of the word "problems" does not convey the dilemmas that IRBs must debate during the course of reviewing human subjects research. We believe the question is one of how the IRB must perform a balancing act to successfully fulfill its mandate. On the one hand, the IRB must act to safeguard the rights of patients/subjects and strike a balance in applying the principles of beneficence, autonomy, and respect for persons that are outlined in the Belmont Report. On the other hand, the IRB must not become a barrier to faculty who seek improvements in the practice and delivery of medical care.

The issues surrounding the securing of appropriate informed consent from subjects are many. They include, but are not limited to, the following issues: a) educational level of populations that may be studied, b) impact of hospitalization on patient/subject comprehension of information presented, c) the legal requirements for information imposed by federal and state regulations which is often conveyed in complex and detailed language, d) the cognitive state of patients/subjects who are asked to join research studies, and e) the timeliness of the consent process as it impacts on patient decision making capacity.

The issues associated with concept of informed consent present as a continuum. Informed consent must be considered in the range of cases starting with potential subjects who have no impairment, either physical or mental, to the other extreme where subjects will be patients who have a severely limited capacity, or no capacity, to provide consent. There are some who argue that truly informed consent is a myth and such consent can never be achieved. The Johns Hopkins IRBs do not subscribe to such an absolute condemnation of consent, as it would prohibit conduct of any research. The authors of the Belmont Report considered this position and rejected it, too.

Clearly, consent issues become more complex and require more discussion as a subject's mental/physical capacity diminishes. Even with the flaws that may be found in current consent processes and documents used in research studies, we submit that consent obtained for participation in research studies is more informed than consent given for routine diagnostic or therapeutic procedures patients undergo as part of general medical practice.

The writers of the Belmont Report recognized that it would be necessary to include subjects with diminished capacity. The Department of Health, Education, and Welfare acknowledged this issue, too, in the August 14, 1979 Federal register announcement "Proposed Regulations Amending Basic HEW Policy of Human Research Subjects", by stating "By finalizing first the regulations applicable to the review and monitoring of all research involving human subjects and covered by these regulations, the Department may then issue only those additional regulations necessary for the protection of specific categories of subjects who may have diminished capacity to consent." The task of IRBs is to determine, and require as it deems appropriate, that additional protections must be built into certain categories of research (i.e. children, prisoners) or into specific, individual research proposals.

Consent issues are magnified when human subjects research is conducted in the emergency room or intensive care units. Patients in emergency care situations often do not have family members in attendance who can either assist in making a decision to join a research study or who can make this decision for a patient. In the small number of research protocols that involve patients with diminished capacity, the Johns Hopkins IRBs apply the methods of obtaining consent currently in use in clinical care settings. Under Maryland state law, next of kin may grant consent to medical care if the patient is incapacitated. Before approval of research in emergency rooms is granted, IRBs must weigh carefully the risks and benefits to the potential subject, along with all of the possible issues associated with obtaining consent. This decision process, though, is not different from the review of any research project that is conducted. It is only that the details involving the emergency situation must be factored into the process.

IRBs have struggled to find, within the Federal regulations, rules that would allow sound scientific research studies to proceed under conditions where consent cannot be obtained. The regulations contain provisions for waiver or alteration of the consent process, but do not contain sufficient guidance to IRBs on this point. Attachment B contains copies of two recent articles from the publication "IRB" which details the efforts of one IRB to achieve a balance between rights of subjects and the need to advance care in their review of an emergency medicine protocol. The struggles the Nebraska IRB faced in reaching its decision on this project are consistent with issues the Johns Hopkins IRBs have had to grapple with in their review of emergency room research proposals.

"Dr. Arthur Caplan... has described current practices in informed consent for emergency room situations as 'a regulatory swamp.' ...Do you agree?"

We believe that the current regulatory standards regarding the ability of IRBs to grant exceptions or waivers to the requirement for obtaining prospective informed consent are not clear with regard to the issue of consent in emergency medicine settings. The regulations allow an IRB to be flexible in its application of the regulations at the time it considers when a waiver or consent exception may be granted, but only to a limited degree. The application of the DHHS regulations must include a determination that the following four conditions are met:

"(1) the research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver or alteration; and

(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation."

Therefore, all IRBs have a strict obligation to review each of these requirements before approving a waiver from the consent requirement for any proposed human subjects research project.

The Johns Hopkins IRB have approved waivers from the requirement for consent only when patients are not denied standard medical care, the research cannot be done without the waiver, the study represents minimal risks to subjects in their medical condition, and the proposed research carries a high likelihood of benefit in the area of improving care. The issues of the types of information to be provided to either the participant or his/family must also be addressed in context of a proposed consent waiver. That different IRBs may apply the regulatory requirements for a waiver from consent in a non-uniform fashion should not be taken to mean that these different approaches or interpretations are unethical. Rather, it reflects the struggle to discuss these issues at a local institutional level.

As Dr. Caplan points out, federal regulations are not consistent between agencies (FDA and DHHS) with regard to consent issues. In the case of DHHS regulations, it is the concept of "minimal risk" that causes IRBs the most difficulty when applied to the evaluation of risks and benefits associated with emergency research. Some individuals argue that "minimal risk" should be evaluated in the context of what is happening to the patient in the emergency room or ICU. For patients receiving aggressive standard therapy and invasive medical interventions, the addition of some research procedures does indeed represent only "minimal risk" compared to standard therapy.

This interpretation of minimal risk may go beyond the original intent of those who drafted the original regulations. Now, however, IRBs are reviewing research proposals in areas not even considered in the 1970s when the original regulations were promulgated. It makes sense to IRBs that a standard of minimal risk that is applicable to a specific patient population is a definition that allows consideration of emergency medicine research proposals. If IRBs are not allowed to interpret this regulatory section on a case-by-case basis, the effect of a strict definition of minimal risk could seriously limit the ability to improve medical practice. We would not characterize this situation as "a regulatory swamp" but, nevertheless, acknowledge that there are no clear cut, useful, and practical published guidelines available to assist an IRB in making decisions on the issue of consent in emergency medical settings when the research involves greater than minimal risk.

"Under what circumstances do you allow informed consent to be waived? Do you allow "deferred consent"? How is it defined. Does it present any special ethical problems?"

Any proposed exception to the requirement for written, prospective consent from subjects requires thorough review and discussion at a convened meeting of the full IRB. This requirement for review and discussion of a proposed consent waiver applies to all research proposals and not just to research conducted in emergency settings.

Requests for waivers are granted rarely at the medical school. In the last two years, there have been only 2 waivers granted by the JHBMC IRB and only 4 waivers granted by the JCCI. To place these figures into context, in the last two years the JHBMC IRB reviewed 406 new human subjects applications and the JCCI reviewed 1193 new human subjects applications. Of the 6 waivers granted by the two medical campus IRBS in two years, only 2 waivers were for protocols involving emergency medicine research. It took several convened IRB meetings and discussions with the investigators before the IRBs voted to approve a waiver.

Neither medical school IRB allows "deferred consent" nor believes it can be considered as a form of "consent". Rather, at this institution we believe that when a waiver from the requirement to obtain written prospective consent is obtained, the patient and/or their next of kin must be informed about the research study into which the patient was enrolled. This does not constitute consent for the original enrollment, for enrollment already occurred.

In the case where a project involves continuing participation of a patient/subject in the research project, it is imperative to ask a patient/family whether they wish to provide consent for the patient to remain in the research study. The procedure for obtaining consent to allow continued participation is modelled after State law with regard to institution of standard medical procedures or therapies employed in emergency medical situations.

"We are particularly concerned about people who may be incapacitated because of head injuries or other conditions such as severe alcoholic stupor. ...Do you share this concern? If so, what can the NIH or the FDA do to impose a more reasonable standard of protection?"

The preceding section indicates we take the rights and welfare of incapacitated patients very seriously. The conduct of research in emergency medical situations is complicated and difficult for many reasons. The reasons include the physical setting in which such studies must be conducted, the interactions between medical care staff and researchers, and the inability of the patient to interact with the care givers and/or researchers. These issues are identical to consent issues faced in the delivery of standard medical care in emergency situations. There is precedence in many states, though, to allow institution of medical care in the absence of consent from a comatose patient or consent from their next of kin. We believe that the extension of this concept is applicable to the area of research in emergency medicine.

There are medical conditions that leave a patient unable to consent to participation in a research study. In these circumstances, IRB pre-review of the proposed research protocol is essential to ensure that the validity of the research question and the methodology to be utilized are sound and will lead to an advancement of medical care without increased risk to patients/subjects. In some cases, next-of-kin are available to serve as a surrogate decision maker for the patient. In these cases, IRBs require consent from next of kin before enrollment of the patient. In true emergency situations, however, next of kin may be unavailable and delay in institution of a therapy, whether standard medical care or experimental therapy, may result in death of the patient.

In these circumstances, we believe IRB review of the project provides protections to the potential subjects while permitting studies to be conducted when such studies are aimed at improving care for desperately ill patients. An investigator must provide sound justification to the IRB before a decision is made to allow initiation of a research study and before a waiver from the requirement to obtain prospective informed consent can be granted. When the benefits and risks of a proposed study appear to be favorable to the patient and the project is designed adequately to obtain an answer to the clinically important question being addressed, we believe that a waiver from the consent requirement is defensible.

The comment from the Subcommittee regarding some patients who "became unwitting subjects in clinical trials" implies that being in a research study is presumptively a bad thing. We disagree with this perception. The stimulus for emergency medicine research is that physicians are dissatisfied with the effectiveness of standard emergency care. The experimental therapy would not be proposed if it was not believed that it offered a chance for improved therapy. IRB review of such proposals serves to temper overly optimistic expectations of some investigators.

If one takes the absolute position that research cannot take place without the consent of an individual, or their legally authorized representative, then progress in this important area of care of desperately ill or injured patients in the U.S. will be severely hampered. Although one can reasonably expect that there will always be an individual who would object to having research done on them without their consent, it is also reasonable to expect that there will be an equal or greater number who would object to being precluded from participating in, or being denied the fruits of, such research. Although there are little data available on this issue, Attachment C reports the results of an examination of the question of whether people objected to their next of kin being in an emergency medicine protocol without first obtaining prospective informed consent.

The public needs reassurance that this category of research has oversight, has peer review, and is limited to a very narrow category of research studies. Publicity surrounding the revelations about research done in the past where radioactive compounds were given to individuals without their consent or without full disclosure illustrates the problem of perceived risk and abrogation of patient rights. It is possible that the reaction to the "radiation" studies was prompted by the fact that these subjects were not told about the studies, were misled about the true purpose of the study, or that the research was performed for reasons unrelated to the patient's condition. We wish to make it clear that such studies would <u>not</u> be approved by the Hopkins IRB.

Federal regulatory guidance on the kinds of studies allowed to be conducted without first obtaining consent of a subject would reinforce to the public that subject protections do exist. We would suggest that such regulatory guidance be premised on the principle that the studies would lead to a better understanding of, or therapy for, the condition that results in the patient's inability to provide consent (i.e. head trauma, stroke, cardiac arrest). Johns Hopkins IRBs and researchers, and we believe all researchers, understand that they need the faith and cooperation of the public to be allowed to carry out human subjects research. Regulatory guidance that can foster an open atmosphere for the conduct of human subjects research would be one step in removing the perception that the public are just "guinea pigs"; rather, they are partners in the development of improved medical care through research and their rights as research subjects are given careful attention.

Cases related to consent issues associated with research protocols have rarely been litigated. In the few reported cases, there is little guidance on how to resolve the consent issues that were raised. In our experience, IRBs and investigators are aware of the importance of informed consent and stress the need to comply with this ethical dictum. We do not believe that these consent issues require institution of new levels of bureaucracy in the hope that "additional protections" will be afforded to research subjects. Rather, we believe there should be clarification of existing rules based on a clear consensus of societal goals with regard to human subjects research in the area of emergency intensive care.

The IRB review process has worked well to limit the abuses seen in the past. We acknowledge that the Subcommittee has received information about individual research protocols that are being conducted under questionable circumstances. However, when placed in the context of the vast array of the ethically and scientifically sound medical research being conducted with human subjects, such deviations from the norm can be seen to be just that - deviations. Peer review of human subjects research is clearly working, but just as clearly improves when it has continuing input scientists, lay people, ethicists, and representatives from the government.

Investigators, institutions, and IRBs that deliberately ignore the rights and welfare of human subjects should be called to task. Such cases, though should not be used as a means for painting all research with the label "unethical."

In summary, we believe that this Subcommittee has correctly focused attention on an area that requires further discussion, debate, and guidance. IRBs have been dealing with issues concerning informed consent in research settings for years. What is needed now that the human subjects regulations have been in practice for more than a decade, and as medical practice becomes more sophisticated, is open dialogue and discussion on what society believes protects the rights of individuals who are in emergency medical situations and faced with the possibility of becoming a research subject.

I hope that this testimony will provide stimulus for the continued debate and resolution of these timely and problematical issues.

Sincerely yours,

Gary Briefel, M.D.
Chairman, JHBMC IRB
c/o 3B.79 Asthma & Allergy Center

GB/
Enclosures
CC: Dr. David A. Blake (Executive Vice Dean, School of Medicine)
Dr. James Block (President - JHH & JHHS)
Dr. Gary Goldstein (President, Kennedy-Krieger Institute)
Dr. Carol Gray (Dean, School of Nursing)
Dr. Thomas R. Hendrix (Chairman - JCCI)
Dr. Michael M.E. Johns (Dean, School of Medicine)
Mr. Ronald Peterson (President - JHBMC)
General Counsel's Office

ATTACHMENT A

Dr. Gary Briefel's Testimony

Form A - Revised 12/92

RESEARCH PROJECT NOTIFICATION (RPN)
(New Project or Third Year Renewal)

JOINT COMMITTEE ON CLINICAL INVESTIGATION AND [redacted] MEDICAL CENTER-IRB
Johns Hopkins Bayview

RPN No. _____
Investigator(s) _____
DO NOT WRITE IN THIS BLOCK

Principal Investigator: _____ Dept. _____
(Must be a Faculty Member)

Co-Investigators: _____

TITLE OF PROJECT: _____

Answer ALL of the following questions:

YES	NO	
☐	☐	Will licensed drugs or diagnostic reagents be administered to human subjects?
☐	☐	Will Investigational New Drugs be used? If yes, provide IND# _____. Is IND# held by the a) Sponsor ☐; or b) Investigator ☐. If the IND# is held by the sponsor, provide the investigator's brochure summarizing the preclinical data and testing (or provide an explanation of why this is not available) and a copy of the sponsor's protocol. If the IND# is held by the investigator, provide a copy of the application submitted to the FDA. Submit a drug data sheet (Form E) as part of the RPN application.
☐	☐	Will Investigational Devices be used? If Yes, provide IDE# _____. Is IDE# held by the a) Sponsor ☐; or b) Investigator ☐. Provide either the investigator's brochure summarizing the preclinical data and testing, or provide an explanation of why this is not available. If the IDE# is held by a sponsor, provide a copy of the sponsor's protocol.
☐	☐	Will subjects be exposed to any source of ionizing radiation (x-rays, radioisotopes, radiotherapy, etc.)? If YES, complete and attach the appropriate form.
☐	☐	Will the project involve research in pregnant women or fetal tissue?
☐	☐	Will any infectious or biohazardous agents be used? If Yes, append details of containment procedures.
☐	☐	Will children be used as subjects? If YES, supply details of assent procedures to be used.
☐	☐	Is this a multi-center collaborative project?
☐	☐	Is the project being submitted for funding by any agency of the Public Health Service? If YES, attach a copy of the "Human Subjects" explanation ONLY from the Methods of Procedure section of the grant application.
☐	☐	Do *any* of the participating investigators serve as a consultant to the sponsor, or manufacturer, or owner of the test article? If YES, has a written disclosure been submitted to the appropriate department director?
☐	☐	Do *any* of the participating investigators (or their immediate family) have an equity and/or royalty relationship with the sponsor of the project, or manufacturer, or owner of the test article? If YES, submit a written statement of disclosure to the designated official for review of conflict of interest at the investigator's institution of primary appointment.

Identify subjects to be recruited (types of patients, volunteers, students, employees, etc.):

Study Location (JHH, FSKMC, GRC, NIDA, JHAAC, etc.) _____ Age range: _____
Project will involve: Males only _____ Females only _____ Males & Females: _____
NOTE: If either sex is excluded from enrollment, in the text provide scientific rationale to justify the exclusion.
Source of Patient population (in-patient or OPD): _____
Source of normal volunteer population: _____
NOTE: If normal subjects are to be enrolled, include in the research plan a description of the recruitment procedure and specify any remuneration to be provided.
Number of subjects (experimental and controls) expected to be enrolled: 1st year _____ Total study _____

RESEARCH PLAN
(Complete Sections I, II, III, and IV)

I. Specific Research Question(s) to be Addressed by this Protocol:

SECTIONS II, III, and IV of the application should be detailed in an attachment of NO MORE THAN three pages and provided in consecutive order. Submission of a more extensive description is not an acceptable fulfillment of this requirement and will be returned. Supporting data, relevant publications, etc. may be included as an appendix.

II. RATIONALE:	Briefly state the problem, the present knowledge relevant to it, and the aims of the proposed study as relating to the research questions.
III. PROTOCOL:	Briefly describe the experimental design. Identify all procedures and carefully distinguish those which are experimental from those which are routine care. Briefly describe the experimental design, including methods to assess results. If the protocol involves use of questionnaires or interview instruments, a copy of these documents must be filed with this application.
IV. RISKS:	Describe major and minor risks and their expected frequency. Detail any measures that will be taken to minimize and deal with the risks. In studies without therapeutic benefit to subjects, both minor risks and possible late effects from participation in the study should be included.
V. CONSENT PROCEDURES:	CONSENT MUST BE OBTAINED FROM ALL PARTICIPATING SUBJECTS (OR THEIR PARENTS/GUARDIANS). IF YOU BELIEVE THAT CONSENT CANNOT REASONABLY BE OBTAINED FOR THIS STUDY, JUSTIFY THIS REQUEST IN DETAIL. An original and one photocopy of the proposed consent document should be included. All consent explanations must be typed on the Blue Form C (revised 1993). Guidelines for writing a consent form are attached to this application form.

ANY PROPOSED ADS FOR RECRUITMENT OF SUBJECTS/PATIENTS MUST BE REVIEWED BY THE COMMITTEE OR IRB *PRIOR* TO PUBLICATION IN THE NEWSPAPERS OR POSTING ON INSTITUTIONAL BULLETIN BOARDS. INCLUDE A COPY OF ADVERTISEMENT WITH THE RPN APPLICATION.

YES ☐ NO ☐ Is *any* support for the project anticipated? If YES, complete the appropriate sections below:

_____ Financial/equipment support
Sponsor name: _____
Proposed Start Date: _____
Sponsor #: _____ (if known)

_____ Drugs/devices only supplied by manufacturer
Manufacturer _____

_____ Clinical Research Center:
Specify: Adult, Pediatric, OPD, Gerontology _____

_____ Other (explain): _____

_____ None (explain): _____

If you do not anticipate any support, and the project involves clinical procedures conducted primarily for research purposes, provide an explanation of the expected source of payment for these procedures. The Committee seeks reassurance that patients will not be put to financial risks from participation in the research study.

_____ _____
Signature of Principal Investigator Date

_____ _____
Faculty Title Phone

_____ _____
Signature of Department Chairman Date

Completed, typed forms should be mailed to:
THE OFFICE OF THE JOINT COMMITTEE ON CLINICAL INVESTIGATION
The Johns Hopkins University School of Medicine
Room 129 S/M Administration Building
720 Rutland Avenue, Baltimore, Maryland 21205
For additional information, call 955-3008

or

THE ~~FRANCIS SCOTT KEY~~ Johns Hopkins Bayview Medical Center INSTITUTIONAL REVIEW BOARD FOR HUMAN RESEARCH
Room 3B-79
5501 Hopkins Bayview Circle
Baltimore, Maryland 21224
550-1853

Revised 12/92

GENERAL GUIDELINES FOR PREPARING THE

"EXPLANATION OF RESEARCH PROJECT TO SUBJECT" SECTION OF

A CONSENT FORM FOR CLINICAL INVESTIGATION

CONSENT FORM EXPLANATIONS FOR RESEARCH PROJECTS MUST be typed on a standard blue Form C (revised 5/91). The explanation should be brief and concise. The recommended type style should be as large as possible to facilitate ease of reading by the subjects. We recommend a type size >12 characters/inch. If continuation pages are necessary, the explanation may be continued using a plain sheet of white paper. Additional pages should be numbered clearly and should contain both the title of the project and the name of the principal investigator typed at the top of the page.

Paragraph headings should be used to organize the explanation. A sample consent form is attached. The sample illustrates how to organize the explanation of the project to include all of the required elements of a consent form.

The explanation should be written as if the investigator were speaking to the patient; avoid speaking for the patient with statements like "I understand that...". The Committee believes that use of first person in the explanation is coercive and puts words in the mouths of subjects. Patients/subjects may not understand an explanation written in first person, but they may be too embarrassed to ask questions. It is preferable to have the explanation written in second person. In the interest of simplicity, use separate consent forms for subject subgroups. Different benefit-risk considerations for subjects should be explained on separate forms.

The explanation should be written at an appropriate reading level for the population. There are standard computer programs available to assist in grading readability of consent forms. We recommend one in particular, "Corporate Voice" from Scandinavian Systems. If you need assistance in grading the reading level of the consent text, contact the Committee staff for assistance.

If you have any questions about the guidelines for writing consent forms, please call either the JCCI staff at 955-3008 or the FSKMC IRB staff at 550-1853.

5/91

Form C (Revised 5/91)

SAMPLE CONSENT FORM

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Francis Scott Key Medical Center, etc.)

Patient I.D. Plate

Title of Research Project:

REQUIRED ELEMENTS OF INFORMED CONSENT:
MOST CONSENT DOCUMENTS MAY BE COMPRISED OF FIVE PARAGRAPHS WHICH ADDRESS THE FOLLOWING ISSUES:

Explanation of Research Project to Subject:

PURPOSE OF STUDY:

Explain the purpose of the research project.
Explain how/why the patient/volunteer qualifies for the study and inform him/her that he/she is being asked to join the study.

PROCEDURES:

Briefly explain the study design, as well as the procedures the subject will undergo if he/she agrees to join the study.
Explain how treatment groups will be assigned.
IF RANDOMIZATION WILL DETERMINE TREATMENT ASSIGNMENT, EXPLAIN IT IN READILY UNDERSTANDABLE TERMS. It is suggested the subject understand that randomization means that treatment will be determined either by drawing a card, drawing a number or flipping a coin.
Specify the number of required hospital visits, clinic visits, inpatient or outpatient actual time commitment involved in participation, number of venipunctures, amount of blood to be drawn, (in household measures), etc.
Clarify what will be done to the subject solely for research purposes and/or what is innovative in the project.

RISK/DISCOMFORTS

For studies that offer potential benefit to subjects, describe risks unique to the study. For major risks, estimate their severity and likelihood, or compare these risks with natural risks that are understood by most patients.
For studies of no potential benefit to the subject, list all risks which are more than minimal. In this case, minimal risk is defined as not greater, considering the probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine medical tests, which are otherwise indicated.

BENEFITS

State potential benefits of participation for the subject:
DO NOT OVERSTATE BENEFITS WHEN SUCH ARE NOT REALISTIC EXPECTATIONS.
If a subject will not benefit from participation, clearly state this fact.
State possible general benefits for science or for other patients with similar diseases, or for the population at large (if applicable).
If applicable, outline remuneration amount and payment procedure, including penalties for failure to complete the study.

ALTERNATIVES TO PARTICIPATION: (May be omitted for normal volunteer studies)

Explain realistic alternatives to participation; specifically, state what treatment will be offered or recommended if patient declines to participate.

THIS CONSENT FORM CONTINUES ON THE REVERSE SIDE

If you sign this form, you are willing to join the research project described to you on the other side of this page. Your doctors, or the investigators, did explain the other kinds of treatment that are available to you and to others. You should ask the principal investigator listed below any questions you may have about this research study. You may ask him/her questions in the future if you do not understand something that is being done. The investigators (or doctors) will share with you any new findings that may develop while you are participating in this study.

The records from this research study will be kept confidential and will not be given to anyone who is not helping on this study, unless you agree to have the records given out. If the study uses a new drug or device that is under the jurisdiction of the Food and Drug Administration (FDA), the FDA government officials may look at the relevant part of your medical records as part of their job to review new drug and device studies.

If you want to talk to anyone about this research study because you think you have not been treated fairly, or think you have been hurt by joining the study, or you have any other questions about the study, you should call the principal investigator,_____, at _____, or call the Office of the Joint Committee on Clinical Investigation at 955-3008 or call The Francis Scott Key Medical Center Institutional Review Board for Human Research at 550-1853. Either the investigator or the people in the Committee office or IRB office will answer your questions and/or help you to find medical care for an injury you feel you have suffered. The Johns Hopkins University, The Johns Hopkins Hospital, The Francis Scott Key Medical Center,_____and the Federal Government do not have any program to provide compensation to you if you experience injury or other bad effects which are not the fault of the investigators.

You may withdraw from the research study at any time. Even if you do not want to join the study, or if you withdraw from it, you will still have the same quality of medical care available to you at Johns Hopkins or the Francis Scott Key Medical Center.

If you agree to join this study, please sign your name below.

NOT VALID WITHOUT THE COMMITTEE OR IRB STAMP OF CERTIFICATION

VOID ONE YEAR FROM ABOVE DATE

RPN NO. _____

_____

Subject's signature
(including children, when applicable)

_____

Signature of Parent or Guardian (when applicable)

_____

Witness to Consent Procedures*

_____

Signature of Investigator

_____

Date

*Optional unless subject is illiterate, or unable to sign.

NOTE: Signed copies of this consent form must be a) retained on file by the Principal Investigator; b) deposited in the patient's medical record; and c) given to the patient.

Revised: 5/91

Form C (Revised 6/93)

CLINICAL INVESTIGATION CONSENT FORM

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Francis Scott Key Medical Center, etc.)

Patient I.D. Plate

Title of Research Project:

Explanation of Research Project to Subject:

THIS CONSENT FORM CONTINUES ON THE REVERSE SIDE

If you sign this form, you are willing to join the research project described to you on the other side of this page. Your doctors, or the investigators, did explain the other kinds of treatment that are available to you and to others. You should ask the principal investigator listed below any questions you may have about this research study. You may ask him/her questions in the future if you do not understand something that is being done. The investigators (or doctors) will share with you any new findings that may develop while you are participating in this study.

The records from this research study will be kept confidential and will not be given to anyone who is not helping on this study, unless you agree to have the records given out. If the study uses a new drug or device that is under the jurisdiction of the Food and Drug Administration (FDA), the FDA government officials may look at the relevant part of your medical records as part of their job to review new drug and device studies.

If you want to talk to anyone about this research study because you think you have not been treated fairly, or think you have been hurt by joining the study, or you have any other questions about the study, you should call the principal investigator,_____, at _____, or call the Office of the Joint Committee on Clinical Investigation at 955-3008 or call The Francis Scott Key Medical Center Institutional Review Board for Human Research at 550-1853. Either the investigator or the people in the Committee office or IRB office will answer your questions and/or help you to find medical care for an injury you feel you have suffered. The Johns Hopkins University, The Johns Hopkins Hospital, The Francis Scott Key Medical Center,_____and the Federal Government do not have any program to provide compensation to you if you experience injury or other bad effects which are not the fault of the investigators.

You may withdraw from the research study at any time. Even if you do not want to join the study, or if you withdraw from it, you will still have the same quality of medical care available to you at Johns Hopkins or the Francis Scott Key Medical Center.

If you agree to join this study, please sign your name below.

NOT VALID WITHOUT THE COMMITTEE OR IRB STAMP OF CERTIFICATION

VOID ONE YEAR FROM ABOVE DATE
RPN NO. _____

_____
Subject's signature
(Including children, when applicable)

_____
Signature of Parent or Guardian (when applicable)

_____
Witness to Consent Procedures

_____
Signature of Investigator or Approved Designee

_____
Date

*Optional unless subject is illiterate, or unable to sign.

NOTE: Signed copies of this consent form **must** be a) retained on file by the Principal Investigator; b) deposited in the patient's medical record; and c) given to the patient.

Revised: 6/93

APPENDIX F

THE JOHNS HOPKINS HOSPITAL AND
THE FRANCIS SCOTT KEY MEDICAL CENTER
INVESTIGATIONAL DRUG
DATA SHEET

PATIENT'S NAME AND HISTORY NO.

In accord with the policy on investigational new drugs, an Investigator must place a completed Investigational Drug Data Sheet(s) in the medical chart each time a patient is admitted for study drug.
(Form to be placed in front section of medical chart)

Principal Investigator:

Office Phone: Home Phone:

Co-Investigators:

Authorized Physician(s):

Protocol Title:

RPN No: APPROVED/RENEWED (date):

1. Drug Name (Name to be used in prescribing and labeling):

2. Drug Synonyms:

3. Dosage Form(s) and Strength(s) Used in This Study:

4. BASED ON TERATOGENICITY, CARCINOGENICITY, MUTAGENICITY, AND REPRODUCTIVE TOXICITY DATA DOES THE SPONSOR OF THE IND REQUIRE SPECIAL HANDLING PRECAUTIONS (i.e. as currently required for chemotherapeutic agents) for PHARMACISTS AND NURSES? If yes, describe in detail.

5. Usual Therapeutic Dose and Range for this Study:

over

THE JOHNS HOPKINS HOSPITAL AND
THE FRANCIS SCOTT KEY MEDICAL CENTER
INVESTIGATIONAL DRUG
DATA SHEET

---

6. Person/Pharmacy Responsible for Dispensing Drug(s) for this Study:

7. Expected Therapeutic Effects:

8. Possible Adverse Effects:

9. Directions for Preparing Drug:

10. Route and Rate of Administration:

11. Special Instructions:

This Data Sheet Last Revised by Investigator/Pharmacist (date)_____

(#JHHX250495 Form Revised 10/89)

APPENDIX I

THE JOHNS HOPKINS HOSPITAL

INVESTIGATIONAL DEVICE AUDIT FORM

FOR STORAGE, DISPOSITION, AND RECORD KEEPING

Principal Investigator_____

Protocol Title_____

_____

_____

RPN #_____ Name of Auditor_____Date_____

Name (s) of Device_____

Authorized Users_____

_____

The auditor will attach a comment regarding "NO" responses.

	YES	NO
DEVICE AND PROTOCOL INFORMATON		
1. The IDS has received a copy of the RPN.	_____	_____
DEVICE STORAGE AND SECURITY		
1. Access to the device is controlled.	_____	_____
2. Device is located_____		
DEVICE RECEIPT RECORDS		
1. The manufacturer/sponsor's name and address are on file (phone number is recommended also).	_____	_____
2. Copies of device invoices are maintained by the investigator.	_____	_____
3. Written documentation of device received includes: shipment date, device name, quantity received, batch number or code number, device label includes statement "Caution: Investigational Device.Limited by Federal Law to Investigational Use.", date and initials of person documenting receipt of shipment, and condition of device(s) upon receipt.	_____	_____
4. The investigator has written documentation of any discrepancies between the invoice and what was actually received.	_____	_____
5. If applicable, the investigator has the expiration date of the device on file.	_____	_____

DEVICE DISPOSITION/ADMINISTRATION RECORDS

Written documentation of exposure of each subject to the device includes the following:

	YES	NO
1. Date used/implanted.	_____	_____
2. Patient initials.	_____	_____
3. Quantity used/implanted.	_____	_____
4. Batch number or code number.	_____	_____
5. Initials of physician who used/implanted device.	_____	_____

DEVICE ACCOUNTABILITY

The quantity of device(s) received minus the quantity of device(s) used/implanted (or otherwise accounted for) must equal the quantity of device(s) in stock. An on-going record of this balance shall be maintained by the investigator.

1. The investigator's device accountability records are constructed to satisfy these requirements.	_____	_____
2. When an inventory count is done, the balance in stock equals the balance recorded in the investigator's records.	_____	_____

cc: Principal Investigator
P & T Committee
JCCI

9/88 rmt/bls

APPENDIX H

Guidelines for Radiation Statements

When a participant in a research study is subjected to ionizing radiation exposure (other than that which is incidental to standard medical management of the participant) the consent form must make a full and meaningful disclosure of the exposure. The consent form statements should include:

a) A comparative risk assessment statement. The following statement is suggested : *"The radiation exposure you will receive from participating in this study is equivalent to an exposure of _____" rems to your whole body. Naturally occurring radiation (cosmic radiation, radon, etc.) produces whole body radiation exposures of about 0.3 rem per year. Occupationally exposed individuals are permitted to receive whole body exposures of 5 rems per year."*

b) If women of child bearing age are included in the protocol, they must be informed that they can participate only if they are certain that they are not pregnant†. The following statement should be used: *"If you are female, you may participate in this study only if you are certain you are not pregnant. A pregnancy test will be performed at your request. If you become pregnant (or suspect pregnancy) before this study is completed, you must inform the investigator. "*

*Please note that effective dose equivalent values should be summed for all procedures involving radiation exposure. Make sure that values are expressed in the appropriate units (use rem, 1 rem = 1000 mrem) in the above consent form statement.

†Pregnant subjects are typically excluded from protocols using ionizing radiation but conditions could exist where pregnant subjects may be involved. In such rare instances that pregnant subjects (patients or volunteers) are recruited into a protocol using ionizing radiation, their involvement will be reviewed on a case by case basis.

For assistance in dosimetry or consent statements, contact:
James Frost, MD, PhD, (955-8449),
Thomas Beck, ScD (955-2684) or
Stanley Wadsworth, MS (955-3710).

Request for Use of Ionizing Radiation in Human Research

RPN#_____TITLE _____

_____

_____

Send completed form and RPN form to the Office of the Joint Committee on Clinical Investigation, Room 129, School of Medicine Administration Building. Return only those pages pertinent to the protocol; dose tables are for investigators convenience only.

SECTION I. Subject Population

		Healthy Controls	Subjects with Disease
A.	Number of Subjects	_____	_____
B.	Age Range	_____	_____
C.	Sex	_____	_____
D.	Nature of Disease		_____
E.	Will pregnant women be excluded?	_____	_____

SECTION II. Radioactive Materials

Do all radionuclide administrations constitute standard medical management of each individual?

Yes____

No ____ If no, attach *Worksheet for Radionuclide Radiation Exposure.*

SECTION III. External Radiation

Do all external radiation exposure procedures constitute standard medical management of each individual?

Yes_____

No_____ If no, attach *Worksheet for External Radiation Exposure.*

SECTION IV.

A. Procedures involving radiation will be conducted at (check all that are appropriate):

_____ Nuclear Medicine (JHH or FSK) _____ MIRU (JHH)

_____ Radiation Oncology (JHH) _____ Radiology (JHH or FSK)

_____ Other (specify): _____

B. I agree to abide by all regulations promulgated by the Johns Hopkins Medical Institutions' Joint Committee on Radiation Control.

Signature_____ Date_____

Worksheet for Radionuclide Radiation Exposure

RPN#_____TITLE_____

_____

_____

I. Radiopharmaceutical	Isotope A	Isotope B	Isotope C
A. Isotope (e.g. ^{99m}Tc)			
B. millicuries per administration			
C. Administrations per subject			
D. Route of administration (e.g., IV)			
E. Chemical/physical form			
F. Active ingredient			
milligrams per administration			

II. FDA status of radiopharmaceutical	Isotope A	Isotope B	Isotope C
A. Well established use			
B. New Drug Application			
C. Investigational New Drug Application (give IND No.)			
D. Not FDA approved for intended use or route of administration:			

III. Sterility and Pyrogenicity	Isotope A	Isotope B	Isotope C
A. Is material supplied sterile?			
B. Is material supplied pyrogen free?			

C. If the material is <u>not</u> supplied sterile and apyrogenic, attach a description of methods that will be used to assure sterility and non-pyrogenicity.

IV. Radiation Dosimetry	Isotope A	Isotope B	Isotope C
A. Critical Organ*			

*Specify the organ that will receive the highest radiation absorbed dose.

B. For standard radiopharmaceuticals administered by standard routes: List the product of effective dose equivalent per millicurie administered and the activity administered in millicuries for each isotope below. Effective dose equivalents per millicurie may be obtained from Table 1, the package insert or another publication. Doses shall be summed for the total number of administrations for each isotope.

	Isotope A	Isotope B	Isotope C
Effective Dose Equivalent (H_E)	_____	_____	_____

C. For non-standard radiopharmaceuticals or non standard routes of administration, list organ doses as follows:

Organ	W_i	Isotope A (mrem)	Isotope B (mrem)	Isotope C (mrem)
Gonads	0.25	_____	_____	_____
Breasts	0.15	_____	_____	_____
Red Bone Marrow	0.12	_____	_____	_____
Lungs	0.12	_____	_____	_____
Thyroid	0.03	_____	_____	_____
Bone Surfaces	0.03	_____	_____	_____
Critical Organ* _____	0.06	_____	_____	_____
Other† _____	0.06	_____	_____	_____
Other† _____	0.06	_____	_____	_____
Other† _____	0.06	_____	_____	_____
Other† _____	0.06	_____	_____	_____

* The organ with the highest radiation dose, other than listed organs.
† Refers to the four remaining organs with the highest doses (e.g., liver, kidneys, spleen, brain, thymus, adrenals, pancreas, stomach, small intestine, upper large intestine, and lower large intestine, but excluding skin and extremities).

Worksheet for External Radiation Exposure

I. **Diagnostic X-Ray Procedures:**

A. Types of Procedures:

Procedure:	Body Region	Repetitions*
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

*List number of repetitions of imaging procedure for each study participant over duration of protocol.

B. Radiation Dose Effective dose equivalents (H_E) for some conventional radiographic procedures and for computed tomography in Tables, 2 and 3, respectively. If procedure is not listed, obtain a dose estimate from Radiology personnel or one of the consultants listed on page 1. H_E values from different procedures may be summed, and added to values from radiopharmaceutical procedures. Include the total H_E (expressed in rem, 1,000 mrem = 1 rem) on radiation risk statement of informed consent . (Do not sum skin entrance doses.)

Procedure:	Eff. Dose Equivalent	Skin Entrance Dose*
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
Total H_E	_____	

* List skin doses only if Effective Dose Equivalent is not available.

II. **Therapeutic Radiation Procedures:** List target doses in rem (cSv):

Procedure	Body Region	Dose/Fraction	# Fractions
Brachytherapy	_____	_____	_____
Teletherapy	_____	_____	_____

ATTACHMENT B

Dr. Gary Briefel's Testimony

IRB
A Review of Human Subjects Research

Volume 15 Number 5 September-October 1993

IRB Review of a Phase II Randomized Clinical Trial Involving Incompetent Patients Suffering from Severe Closed Head Injury
by Ernest D. Prentice, Dean L. Antonson, Lyal G. Leibrock, Timothy K. Kelso, and Thomas D. Sears 1

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CALENDAR 5

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IRB Review of a Phase II Randomized Clinical Trial Involving Incompetent Patients Suffering from Severe Closed Head Injury

by Ernest D. Prentice, Dean L. Antonson, Lyal G. Leibrock, Timothy K. Kelso, and Thomas D. Sears

A multicenter Phase II randomized clinical trial (RCT) to investigate the safety and efficacy of polyethylene glycol (PEG)-conjugated superoxide dismutase (SOD) as a treatment for severe closed head injury was submitted for review to the institutional review board at the University of Nebraska Medical Center (UNMC).

Closed head injury is a major cause of death and disability for several hundred thousand patients worldwide each year. The protocol postulates that during the first 24 hours after injury changes in the cerebral vasculature such as abnormalities of the blood-brain barrier, transient changes in perfusion pressure, and altered autoregulatory responses may be responsible for increasing the extent of cerebral damage following head injury. The mediators of these vascular changes are thought to be oxygen radicals that are produced as a consequence of various metabolic processes activated by the traumatic event.[1-2] One oxygen radical species called superoxide anion radical, which is thought to be generated for at least one hour after the head injury,[3] is considered to be very damaging. PEG-SOD scavenges superoxide anion and, thus, may prevent the continuing cerebrovascular damage caused by this oxygen radical. To date, SOD has been shown to have a positive effect on many vascular abnormalities associated with experimentally induced brain injury in the animal model.[4-6] In a limited Phase II clinical trial involving patients with severe head injury where SOD was conjugated with PEG in order to extend its very short biological half life ($t^{1/2}$ = 6 minutes), the results showed that PEG-SOD was generally well tolerated and appeared promising in improving the outcome of patients suffering from severe head injury.[7] This multicenter study was designed to evaluate further the safety and efficacy of PEG-SOD at two different doses.

Ernest D. Prentice, PhD, *is associate dean for research and professor of cell biology and anatomy,* **Dean L. Antonson, MD,** *is associate professor of Pediatrics;* **Lyal G. Leibrock, MD,** *is associate professor of Neurosurgery;* **Timothy K. Kelso, JD,** *is the community representative on the IRB; and* **Thomas D. Sears, MD,** *is associate professor of cardiology, University of Nebraska Medical Center, Omaha.*

Characteristics of the Subject Population

Subjects will be male and female emergency room (ER) patients, 15-70 years of age, who have sustained a severe closed head injury. All subjects must be clinically stable without evidence of severe anoxic intracerebral damage. Female subjects must be sterile or have a negative pregnancy test before administration of the study drug. A maximum of 60 subjects will be enrolled at each of up to 25 study centers.

Experimental Design

The study design is a double blind, placebo-controlled RCT consisting of 3 arms: PEG-SOD 10,000 u/kg, PEG-SOD 20,000 u/kg, or placebo as a single intravenous bolus injection. Because of the unavailability of an identical placebo to PEG-SOD, a third party will prepare the injections and mask the syringe. Randomization codes can be broken in the case of a medical emergency.

All standard therapy that is medically or surgically necessary will be carried out regardless of whether the patient participates in the research. Standard therapy consists of various diagnostic tests such as CT scans of the head and therapeutic interventions such as surgery when indicated, artificial ventilation, and other life support measures. Concomitant with this routine therapy the study drug or the placebo will be administered to participants within 8 hours of the time of injury. According to the protocol, there is a limited therapeutic window. Even though the design of this trial allows the study drug to be administered anytime within 8 hours after injury, it is felt that PEG-SOD should be given as soon as possible after injury in order to achieve the maximum potential efficacy. Some delay, however, is inevitable since the patient will require stabilization (i.e., life-support measures) as well as

various laboratory tests, including a serum pregnancy test as required. It is estimated that eligible patients will be enrolled in the PEG-SOD protocol within a maximum of two hours from the time they present at the ER.

All subjects will be evaluated for an acute period of 14 days with follow-up evaluations at 3 and 6 months. The neurological evaluations are based upon the Glasgow Coma Score (GCS), Glasgow Outcome Score (GOS), and the Disability Rating Scale (DRS). These scales are used to assess the disability of severe head injury patients and provide an indication of the patient's capacity to resume normal occupational and social activities.

Potential Risks Associated with PEG-SOD

PEG-SOD has been shown to be safe and relatively well tolerated in healthy individuals. Isolated incidents of relatively minor adverse experiences such as headache, rash, syncope, and allergic reaction have been reported, but the data indicate an "uncertain" relationship to the study drug. PEG-SOD has also been studied in patients with severe head injury, and reported adverse experiences that are thought to have an "uncertain" relationship to the study drug are ventricular tachycardia and hypertension (less than 1% of subjects). Based upon the clinical data, however, these adverse experiences are likely to be related to the patient's clinical condition rather than the drug.

Proposed Consent Procedure

The investigators will obtain informed consent whenever it is possible from either the patient's legally authorized representative or from his or her next of kin before the study drug is administered. This is referred to as prospective proxy consent. If informed consent cannot be obtained prior to enrollment of the patient in the study, a deferred consent procedure will be used. Deferred consent will be obtained as soon as possible from the subject's legally authorized representative or next of kin. Both the investigator and an independent physician will certify to the IRB within 5 days after the treatment that the patient was confronted by a life-threatening situation necessitating use of the test article, it was not possible to obtain informed consent from the patient or legal representative, and there was no alternative therapy that could offer the patient the prospect of equivalent therapeutic benefit.

IRB Review

The IRB first reviewed the protocol according to the criteria for IRB approval of research as specified in the Food and Drug Administration Regulations 21 CFR 50,56.[8] Since the University of Nebraska Medical Center is a multiple project assurance (MPA) institution that chose to apply the Health and Human Services regulations to all human subjects research regardless of funding source, it was also necessary to consider (HHS) Regulations 45 CFR 46.[9] Approval criteria in the HHS regulations are, however, essentially identical to FDA requirements. In the opinion of the IRB, the protocol met all of the approval criteria specified by these regulations with the exception of the requirement for prospective written informed consent, which must be obtained from either the subjects or their legally authorized representatives unless justification exists to support a waiver. Since the patients will be incompetent and a legally authorized representative may not be available for every patient, the IRB decided it was necessary either to restrict the subject population to only those patients with a legal representative who could give prospective proxy consent or to grant an exception to the informed consent requirement. After considerable discussion, the IRB finally concluded that any restriction of the subject population based upon the availability of a legal representative would unfairly deprive severely injured patients of the opportunity to gain a potential therapeutic benefit that could only be derived from participating in this clinical trial. The board therefore decided to grant an exception to the requirement of prospective informed consent, providing such an exception could be justified under *both* 45 CFR 46.116(d) and 21 CFR 50.23(a), which specify the conditions that must be met for a waiver of informed consent. Since these conditions were not written to accommodate research in emergency settings, the IRB reviewed the available literature and consulted with legal counsel in order to prepare the following analysis.

Analysis of Compliance with 45 CFR 46.116(d)

Under 46.116(d), the IRB can waive the requirement to obtain prospective informed consent from either the subject or his or her legally authorized representative providing four conditions are met. The IRB analyzed the protocol's compliance with each of these conditions.

The research involves no more than minimal risk to the subjects. Using a relative standard of minimal risk based upon the clinical status of the subject the IRB determined that the research involved no more than minimal risk to the subject. In reaching this decision, the board applied the concept of "minimal differential (incremental) risk," which is based, in part, upon a concept of risk assessment proposed by Abramson and colleagues[10] for use in resuscitation research on comatose patients. This means the board concluded that the difference between the potential risk to the subject of an undesirable outcome when standard accepted therapy alone is used to treat the subject's life-threatening condition versus the risk of an undesirable outcome when the experimental therapy, i.e., PEG-SOD, is added to standard therapy is minimal.

Severe closed head injury is a major cause of death and disability. The administration of PEG-SOD combined with standard therapy may improve the neurological outcome in those subjects who are randomly assigned to PEG-SOD. According to the randomization scheme, this represents two-thirds of the subjects. The adverse events reported in clinical trials involving PEG-SOD are not considered serious when compared to the risks associated with the clinical status of the patient, which include severe brain damage and death. Therefore the board, using a relative standard of minimal risk, decided that the research was in compliance with 45 CFR 46.116(d)(1). This decision is consistent with the position of the Office for Protection from Research Risks, which requires the IRB to find that the risk posed by the experimental procedure to subjects suffering from a life-threatening condition is *no more than minimally* greater than the risk they already face.[11]

The waiver or alteration will not adversely affect the rights and welfare of the subjects. The IRB determined that the rights and welfare of the subject will not be adversely affected in the situation where prospective informed consent cannot be obtained. In the opinion of the IRB, patients would choose to participate in this study if they were competent and apprised of the risk-benefit relationship of the research versus that

associated with the therapeutic alternatives alone. This opinion is based upon the concept of "presumed consent" described by Rosoff[12] under which the investigator is deemed to be acting reasonably by assuming the patient, if competent, would agree to participate in the study in order to achieve the potential therapeutic benefit associated with the PEG-SOD.

The current study, of course, raises the issue of administering a placebo that is unlikely to have any therapeutic effect in the patient population. The administration of the placebo is justified, however, because there is no scientifically valid data to indicate that PEG-SOD offers a *proven* therapeutic benefit and, in addition, all standard accepted therapy will be provided. Since standard therapy will not be withheld, it is presumed that subjects, if competent, would agree to be randomly assigned to PEG-SOD versus placebo. While it is likely that some subjects might prefer to participate in an open label study involving a comparison of the two doses of PEG-SOD without the placebo control, the status of the accumulated scientific data on PEG-SOD is such that an open label study would be premature at this time.

Compliance with 46.116(d)(2) is further supported by the fact that every reasonable attempt will be made to obtain proxy consent from a patient's legally authorized representative or next of kin before the patient is enrolled in the study. A legally authorized representative is defined by HHS and FDA as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation."[13] The term "legally authorized representative" is not, however, defined by Nebraska state law in terms of a hierarchy of individuals who are authorized to provide proxy consent for research participation. For the purpose of nonemergency medical treatment, Nebraska statutes recognize a health care power of attorney and, of course, a court appointed guardian; no other individuals have statutory authority to provide proxy consent for routine nonemergency medical treatment. In the absence of applicable state law, then, the IRB chose to follow the UNMC University Hospital medical staff policy and allow proxy consent to be obtained from an available next of kin according to the following preferred hierarchy: spouse, parent, adult child, and adult sibling. While the medical staff policy allows the proxy consent hierarchy to extend to even a distant blood relative, the IRB decided that such an extension was not warranted in a research project.

During the discussion of proxy consent, the IRB considered the concept of "deferred consent" proposed in 1980 by Fost and Robertson for use in a study involving the evaluation of corticosteroids in the treatment of patients with severe head injury.[14] In that study approved by the University of Wisconsin Center for Health Sciences IRB, the proxies of incompetent patients were notified that an experimental procedure was being used, but requests for proxy consent to the research were deferred until 48 hours after the study was initiated. The rationale for this delay was the assumption that 48 hours after treatment was begun family members would be under less stress and would, therefore, be in a better position to provide informed consent. While the UNMC IRB was equally concerned about the emotional and cognitive aspects of being asked to give proxy consent to a research procedure while under stress, the board agreed with Fost and Robertson, who in replying to Beauchamp stated, "If major risks from research occur during the period of deferral, it becomes less defensible to defer proxy consent during that period since interposition of the proxy might serve to protect the subject."[15] In this study PEG-SOD is administered only once as an IV bolus injection, therefore any potential risks associated with PEG-SOD are immediately incurred by the subject. Under this circumstance the IRB was unwilling to approve any deliberate delay in obtaining proxy consent.

In the situation where prospective proxy consent cannot be obtained before a patient is enrolled in the study, the investigator proposed to obtain what is referred to in the protocol as "deferred consent." While this consent procedure did not involve any deliberate delay in soliciting consent, the deferred consent form was written in a prospective proxy consent style which nonetheless implied that consent was being given for interventions that had already taken place. The IRB, however, objected to the use of this interpretation of deferred consent on the same grounds articulated by Miller, who stated, "The notion of deferred consent makes little sense. One cannot consent meaningfully to something that has already happened. Consent implies the possibility of refusal."[16] After review of the literature, the board decided to ask the investigator to use a deferred consent procedure defined by the Brain Resuscitation Clinical Trial II Study Group as informed consent or permission to continue being involved as a research subject after having been enrolled without either informed consent or permission.[10] In addition, the IRB decided to describe the new consent procedure as "proxy informed consent for continued participation in research" as opposed to using the term "deferred consent." This decision is consistent with Beauchamp's reluctance to use the term "consent"

The UNMC IRB approved the PEG-SOD protocol on 29 April 1993 pending receipt of specific clarifications and consent document modifications from the investigator. This paper was submitted to IRB: A Review of Human Subjects Research *on 22 June 1993. On 12 July 1993, the IRB was informed by the sponsor that the FDA was re-evaluating its position relative to deferred consent and that this consent procedure should no longer be used. According to the sponsor's instructions, patients can be enrolled in the PEG-SOD study only if prospective proxy consent is obtained from the patients' legally authorized representatives in full compliance with 21 CFR 50.20. The sponsor, together with other pharmaceutical companies, expressed their great concern to the FDA since FDA has regularly approved INDs in the past that included a deferred consent procedure. Indeed, FDA has a number of new drug applications (NDAs) on file that include data obtained on subjects where a deferred consent procedure was used. This is, obviously, a very significant problem that may affect the future of ER research. As far as the PEG-SOD study is concerned, subject accrual will be significantly compromised and some severely injured patients will be deprived of the opportunity to obtain the therapeutic benefit that PEG-SOD potentially offers. In addition, enrollment may be delayed beyond the estimated two hours from the time the patient first presents to the ER. This delay, in turn, may decrease the potential efficacy of PEG-SOD.*

in the expression of "deferred consent" and, instead, proposed the notion of "nondisagreement" with the decisions that have already been made with regard to participation of the subject in the research.[15]

The research could not practicably be carried out without the waiver or alteration. The IRB determined that the research could not practicably be carried out without the waiver or alteration of informed consent. To restrict research participation to only those patients who have a legally authorized representative or next of kin immediately present would limit the study sample size, introduce potential bias, and deprive some severely injured patients of potential therapeutic benefit that can only be received by participating in the study. In addition, such a restriction would not be consistent with the protocol approved by the FDA and, presumably, other sites participating in this multi-center study.

Whenever appropriate, the subjects will be provided with additional pertinent information after participation. The protocol did not contain any specific provisions for providing subjects with pertinent information about the study once they regained competency. While the IRB assumed the investigator would discuss the study with all subjects who recovered the capacity to resume normal mental function, the board nevertheless decided to require the investigator to obtain written "consent to continue participating in research" from these subjects. This procedure represents both consent to what will occur in the future in the context of research participation and ratification of what has already been done to the subject. Giving such consent implies that the subject believes enrollment in the research without prior consent did not adversely affect his or her welfare, i.e., no wrong or harm was done to the subject by entry into the study.

Considering the high degree of mortality associated with severe closed head injury, it is likely that approximately 30 percent of the subjects in this study will either die or be in a prolonged vegetative state. Therefore, it will not realistically be possible to obtain consent to continue participating in research from all subjects. In addition, some subjects may die before proxy consent has been obtained. In this latter circumstance, the IRB decided that the investigator has an obligation to disclose the pertinent details of the study to the legal representative or next of kin of the deceased. This obligation applies equally for subjects randomized to either PEG-SOD or placebo. Even though administration of the placebo does not represent withholding of treatment and the subject will, therefore, not incur any additional risk as a result of participation in the research, there is nevertheless an ethical obligation to ensure full disclosure.

Compliance with 21 CFR 50.23(a)

An exemption from the FDA informed consent requirement is permitted under 50.23(a) providing the four conditions discussed below are met and certification of compliance is provided to the IRB by both the investigator and a physician who is not otherwise participating in the clinical investigation. If possible this certification should be obtained before use of the test article. The following describes each condition and the IRB's analysis of compliance.

The human subject is confronted by a life-threatening situation necessitating use of the test article. The IRB determined that the prospective subject in this study is confronted by a life-threatening situation necessitating the use of the test article. The test article in this research, PEG-SOD, offers the greatest possibility of therapeutic benefit after all standard therapy has been rendered. Technically, under 50.23(a)(1) the placebo in this study cannot be classified as a potentially lifesaving test article since there is likely to be no therapeutic benefit associated with it and the clinical status of the patient obviously does not require administration of a placebo. As Levine points out, "human subjects are never confronted by life-threatening situations necessitating the use of a placebo."[17] However, it is the position of the IRB that if providing a placebo control is scientifically justified it can be ethically used in an emergency situation when a waiver of informed consent is granted under 50.23(a) *if* standard treatment will not be withheld. Administration of a placebo under the proposed protocol, therefore, would not constitute nontreatment. While the FDA has not confirmed the acceptability of this interpretation of 50.23(a)(1), the IRB was unable to arrive at any other interpretation that would allow an exemption from the FDA informed consent requirements. Since the FDA approved the investigational new drug exemption (IND) for PEG-SOD, the IRB reasonably assumed that FDA had also found the clinical status of the subject and the proposed treatment under the protocol in compliance with 21 CFR 50.23(a)(1).

Informed consent cannot be obtained from the subject because of an inability to communicate with or obtain legally effective consent from the subject. A patient with severe closed head injury is usually unconscious and obviously incapable of giving informed consent. Therefore, the IRB found the study in compliance with 21 CFR 50.23(a)(2).

Time is not sufficient to obtain consent from the subject's legal representative. When a prospective subject with severe head injury is brought into the ER either by ambulance or by life flight he or she may not be accompanied by either a legal representative or next of kin. While the investigators will make every reasonable attempt to obtain proxy consent before the patient is enrolled in the study, it may be necessary to enroll some patients without consent in order to gain the maximum potential benefit within the time frame specified by the therapeutic window. Thus, the IRB found the study in compliance with 21 CFR 50.23(a)(3).

There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. All subjects will receive state of the art therapy as part of their routine care. No available treatments that are medically warranted will be withheld. There is no other approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. Of course, as mentioned previously, the administration of the placebo cannot be considered a life-saving intervention. PEG-SOD, however, has potential therapeutic benefit and may, theoretically, reduce the risk of brain damage and/or mortality in up to two-thirds of the subjects in this study. In addition, since this is a double blind study, the investigator will obviously not know if the subject received PEG-SOD or the placebo. This blinding effectively allows the investigator to operate under the assumption that based upon probability it is more likely that the subject was given PEG-SOD than placebo. The IRB, therefore, found the study in compliance with 21 CFR 50.23(a)(4).

Compliance with 21 CFR 50.23(b)(c)

As previously stated, 21 CFR 50.23(a) requires the investigator to

obtain, where possible, the independent determination (certification) of compliance with the four conditions specified under 50.23(a) before using the test article. If this is not feasible, however, certification of compliance under 50.23(b) should be obtained after using the test article. Pursuant to the requirement of 50.23(c) certification must be submitted to the IRB within 5 working days after the use of the test article. Since the protocol contained an acceptable provision for independent certification, the IRB concluded that the research met the requirements of 21 CFR 50.23(b)(c).

Discussion

Emergency room research involving incompetent subjects is certainly limited, if not prohibited in some cases by HHS and FDA regulations on informed consent. In addition, because the subject is unable to give consent, there are ethical and legal issues associated with ER research that must be addressed by the IRB. The net effect on researchers and IRBs has been to create a reluctance or perceived inability to conduct ER research. Consequently, there has been a less than optimal advancement of scientific knowledge in such areas as head injury treatment and cardiopulmonary resuscitation. Certainly, the UNMC IRB found the task of reviewing the PEG-SOD protocol, in consideration of various regulatory, ethical, and legal constraints, to be both time consuming and frustrating because of a lack of published OPRR/FDA guidance on ER research. However, the board felt they had an obligation to the patient, the investigator, and society at large to overcome any obstacles and approve the protocol if possible.

When the IRB reviewed the PEG-SOD protocol, there was little debate about the risk-benefit relationship of the research, primarily because the design of the study did not involve randomization either to experimental therapy versus standard therapy or to two different experimental treatments in the absence of any standard therapy. PEG-SOD has potential therapeutic benefit, the documented risks are relatively minor, and the board had the luxury of knowing that the subject would not be denied any standard therapy because of participation in research. It is, of course, possible that previously unknown side-effects could occur and some of the reported adverse experiences in clinical trials involving PEG-SOD may ultimately be linked to the drug. In the IRB's judgment, however, the known risks were considered reasonable in relation to the potential benefits to the subject. In the opinion of the IRB, to achieve a favorable balance between potential harm and benefit the potential risks associated with therapeutic ER research involving incompetent subjects must be clearly outweighed or balanced by the prospect of direct benefit to the subject without the need to include societal benefits, i.e. advancement of knowledge. As Cohen reminds us, "Plaintiffs' lawyers are not going to care the slightest about whether people other than the plaintiff are going to receive benefits or not."[18] This is, of course, not usually the case in research involving consenting competent subjects where societal benefit can be used to achieve the necessary balance between harm and benefit. Subjects who are capable of making autonomous decisions can obviously choose to accept risk without personal benefit for their own altruistic reasons.

While the risk-benefit assessment of the research did not prove contentious, the issue of informed consent prompted a great deal of debate. The IRB thought a waiver of prospective informed consent was ethically justified in the PEG-SOD study. However, the board was unsure whether such a waiver could be granted under both HHS and FDA regulations. During analysis of the regulations, it became clear that the FDA requirements were not as problematic as those specified by HHS. Indeed, as mentioned previously, the FDA had already approved the IND for PEG-SOD and, presumably, had found the proposed waiver of informed consent acceptable under the provisions of 21 CFR 50.23(a). On the other hand, OPRR did not review the PEG-SOD protocol in relation to HHS requirements for waiver of informed consent under 45 CFR 46.116(d).

Upon review of 45 CFR 46.116(d), the most significant problem the IRB encountered was whether the PEG-SOD protocol could satisfy the first

CALENDAR

3-4 November The Johns Hopkins Medical Institutions and Johns Hopkins Center for Clinical Trials will sponsor a continuing medical education program, "Ethics and Politics Related to Clinical Trials," to be held in the Thomas B. Turner Building of the Johns Hopkins Medical Institutions in Baltimore. For information: Conference Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Building, 720 Rutland Avenue, Baltimore, MD 21205, (405) 955-2959.

4-5 November The University of Colorado Health Sciences Center and the University of Southern Colorado, in coordination with the NHI and FDA will sponsor a **western workshop**, "Medical Research: Protection of Vulnerable Subjects," to be held at the Radisson Hotel Denver South, Denver, Col. For information: Ms. Mary Peratt, Secretary/IRB, University of Colorado Health Sciences Center, 4200 East 9th Avenue (Box C-290), Denver, CO 80262; (303) 270-7960.

2-3 December The Louisiana State University Medical Center and Xavier University of Louisiana, in cooperation with the NHI Office of Protection from Research Risks, will sponsor a **national animal welfare education workshop** for the **southeastern** region to be held at The Monteleone Hotel in New Orleans (1-800-535-9595). To register: Mrs. Melinda O. Rapp, Division of Animal Care, Louisiana State University Medical Center, 1542 Tulane Avenue, New Orleans, LA 70112; (504) 568-6090; fax (504) 568-4843.

New Publication

The Office of Protection from Research Risks has prepared new guidelines for IRBs evaluating human subjects research. *Protecting Human Research Subjects: Institutional Review Board Guidebook* is available from the U.S. Government Printing Office, stock no. 017-040-00525-3, $31/copy; may be photocopied without restriction. To order: 202-783-3238; fax (202) 512-2250.

condition that must be met for a waiver of informed consent. As per 46.116(d)(1), the IRB must find and document that, "the research involves no more than minimal risk to subjects." Minimal risk is defined as follows: "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[19] Minimal risk is meant to serve as a threshold standard of risk that is based upon the normal risks associated with daily life. However, the regulations do not qualify this standard in terms of the daily life of a healthy individual. According to Mackay, the initial drafts of the definition of minimal risk referred to the daily life of healthy people but the phrase, "healthy people" was dropped because it would have imposed a standard that was overly restrictive when applied to clinical research involving ill people.[20] The IRB, therefore, took the liberty of using a relative standard of minimal risk that is based upon the daily life of a patient with a severe closed head injury. Certainly, the administration of an investigational drug to a healthy individual could never qualify as a minimal risk procedure. However, in consideration of the risks associated with the clinical condition of a severely injured patient, the argument can be made that the threshold of minimal risk is far higher. In this situation, it is possible for an IRB to find that the risk associated with the experimental procedure is no more than minimally greater than the risk the subject already faces. In other words, that the increment of risk associated with the experimental procedure is no more than minimal. Because PEG-SOD has relatively minor side-effects, the IRB concluded that the risk was minimal. As mentioned previously, this use of a relative standard of minimal risk is consistent with the position of OPRR. It is also in agreement with the Informed Consent Position Statement of the Society for Academic Emergency Medicine, which defines minimal risk as "a level of risk equivalent to that which would likely be encountered by individual patients given their current circumstances."[21]

In addition to IRB review, the PEG-SOD protocol was also reviewed by the IRB's legal consultant and the chief executive officer of UNMC. Both reviews focused primarily on questions of institutional liability. There is always the possibility of a lawsuit when a patient is treated without his or her informed consent, particularly in an experimental context. Indeed, malpractice suits have reached epidemic proportions in some areas of the U.S. The IRB was therefore strongly encouraged to adopt measures that would help protect the investigator and the institution should the PEG-SOD research result in a lawsuit. Of course, strictly speaking this is not the role of the IRB. However, consideration of liability often results in a higher standard of subject protection. Accordingly, the IRB emphasized in the documentation of its review both the ethical and the legal imperative that requires the investigator to obtain prospective proxy consent whenever possible. In cases when this is cannot be done the investigator was required to solicit proxy consent for continued participation in research as soon as possible. In addition, the investigator was required to solicit consent from any subject who regained competence. In the opinion of the IRB this clearly demonstrates that the research is being conducted completely above board and, in turn, it is hoped, would confer a reasonable degree of legal protection in addition to adequately protecting the rights of the subjects.

From a legal perspective it is interesting to note that the IRB also required the investigator to inform the relatives of any deceased subject about the study whenever either proxy or direct subject consent could not be obtained. In the opinion of the board, such a notification procedure is ethically warranted but carries with it a distinct legal risk. The IRB recognized the risk and the institution accepted it without any consideration given to the option of not notifying the relatives of the deceased subject. On the other hand, a case could be made that failure to notify the next of kin actually increases the legal risk because nondisclosure could result in characterization of the PEG-SOD research in a negative light.

In conclusion, the IRB and the institution fully support the PEG-SOD study. The research is thought to be justified medically and ethically. In addition, both the IRB and the institution are satisfied that our interpretation of the applicable HHS and FDA regulations is both reasonable and entirely defensible. Admittedly, there is an element of legal risk associated with ER research. However, the need to advance knowledge for the benefit of present and future ER patients demands that investigators and institutions accept this risk.

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An Update on the PEG-SOD Study Involving Incompetent Subjects: FDA Permits an Exception to Informed Consent Requirements

by Ernest D. Prentice, Dean L. Antonson, Lyal G. Leibrock, Vikram C. Prabhu, Timothy K. Kelso, and Thomas D. Sears

In the summer of 1993 the subject of emergency room (ER) research involving incompetent subjects for whom no prospective proxy consent was obtained suddenly erupted out of the "closet" because of a research project commonly referred to as the PEG-SOD study. This study raised the question of whether the FDA and HHS requirements for informed consent are unnecessarily restrictive when applied to ER research. In a recent article published in this journal, we reported on the review and approval of the PEG-SOD study by the institutional review board (IRB) of the University of Nebraska Medical Center (UNMC).[1] The protocol as described in our article is a multicentered Phase II placebo controlled randomized clinical trial (RCT) to investigate the safety and efficacy of Polyethylene Glycol (PEG) - conjugated Superoxide Dismutase (SOD) as a treatment for severe closed head injury. PEG-SOD is postulated to limit cerebrovascular damage following head injury by scavenging an oxygen radical called the superoxide anion, which may be responsible for increasing the extent of brain damage post injury. The prospective subjects are likely to be brought to the ER by life flight or ambulance and will usually be unconscious. According to the protocol, there is a therapeutic window of eight hours, but it is felt that PEG-SOD should be administered as soon as possible after injury to achieve the maximum potential efficacy. Since the therapeutic window is limited and some prospective subjects may not have a legally authorized representative who is readily available to provide proxy consent, the investigators sought to obtain an exemption from FDA informed consent requirements under 21 CFR 50.23(a).[2]

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During the course of review, the IRB analyzed the four conditions of 50.23(a) and determined that an exception to informed consent was justified in the PEG-SOD study, providing the investigator made a reasonable attempt to contact the prospective subject's legally authorized representative or next of kin. Since the UNMC is a multiple project assurance (MPA) institution that chose to apply the HHS regulations across the board without regard to funding source, it was also necessary to determine whether a waiver of informed consent could be granted under 45 CFR 46.116(d).[3] After a detailed analysis, the IRB decided that a waiver of consent was possible under 46.116(d). It should be noted that FDA regulations use the term "exception" to informed consent whereas HHS regulations use the terms "waiver" and "alteration" of informed consent. As far as a subject in the PEG-SOD study is concerned, there is no difference. It should also be noted that while 50.23(a) and 46.116(d) each contain four conditions that must be satisfied, the respective FDA and HHS conditions are distinctly different. This means that at an MPA institution like UNMC, eight different conditions must be satisfied before an incompetent patient can be enrolled in an investigational drug or medical device study where obtaining prospective proxy consent is not possible. Our analysis of compliance with both FDA and HHS regulations is described in the previously mentioned article.

The IRB approved the PEG-SOD study on 29 April 1993. On 12 July 1993 the sponsor notified the IRB that FDA was re-evaluating its position relative to whether an exception to the agency's informed consent requirement could be legally granted in this study. According to the sponsor's communication, FDA decided to prohibit the participation of subjects in the PEG-SOD protocol where it was not possible to obtain prospective proxy consent. The sponsor immediately initiated high level discussions with FDA that also involved the Office of Protection from Research Risks. During the course of these discussions, the Nebraska IRB was asked to provide both FDA and OPRR with a copy of their analysis of the PEG-SOD study in relation to regulatory requirements. This analysis was provided as requested.

OPRR reacted quickly by issuing a report on 12 August 1993 that contained guidelines on waiver of informed consent under 45 CFR 46.116(d).[4] On 8 September 1993 FDA notified the sponsor that incompetent patients could now be enrolled in the PEG-SOD study under the provisions of 21 CFR 50.23(a), as necessary, providing the protocol was amended and the amendments approved by the IRB.[5] Unfortunately, FDA did not provide a regulation-based rationale for their decision. The FDA communication did, however, contain guidelines, hereafter referred to as the FDA PEG-SOD study consent guidelines, that directed the sponsor to specify clearly in the amended protocol the steps that will be followed to ensure that investigators comply with the requirements of 21 CFR 50.23(a) and, in the case of MPA institutions, the requirements of 45 CFR 46.116(d). These guidelines, which were flexible in order to accommodate study site needs and characteristics, centered around the use of an algorithm that the agency defined as "a detailed plan describing a sequence of specific steps that are to be followed to reach a particular decision. Use of an algorithm assures that a uniform path, with consistent decision points and rules, is followed in reaching a conclusion that an exception from informed consent is appropriate." In accordance with FDA instructions, the sponsor developed the framework of an algorithm that was submitted to each study site for local adaptation and IRB approval. The purpose of this article is to describe the IRB-approved algorithm that will be used by the UNMC investigators involved in the PEG-SOD protocol.

Determining Subject Identity. The investigator will make a reasonable and conscientious effort to determine the identity of the prospective subject that will be carried out concurrently with the initial medical treatment of the subject (e.g., clinical stabilization). This effort may include,

as necessary, a physical search of the subject and his/her personal effects, involvement of law enforcement officials who can check Department of Motor Vehicle records, and the interviewing of witnesses to the accident. All procedures used to establish the patient's identity will be documented in the medical record.

Contacting the Subject's Legally Authorized Representative. Once the identity of the subject has been determined, the investigator will make a reasonable attempt to contact the legally authorized representative of the subject. These efforts will include, as necessary, a telephone calling campaign with calls made at least every fifteen minutes over a minimum period of two hours and involvement of local law enforcement officials who will expeditiously visit the subject's residence or establish contact with neighbors and any identified relatives. All contact efforts will be documented in the medical record and no research interventions will be performed on the subject before either prospective proxy consent is obtained from the representative or a period of two hours has elapsed.

Obtaining Prospective Proxy Consent. Upon establishing contact with the patient's legally authorized representative, the investigator will inform the representative of the clinical status of the patient, including the patient's prognosis framed in terms of outcome probabilities that range from full recovery to death. The representative will then be invited to consider providing proxy consent. If the initial contact with the representative is via telephone, the investigator will verbally review the IRB-approved consent document. Any consent obtained by telephone will be subsequently confirmed in writing.

Obtaining an Exception to Informed Consent under 21 CFR 50.23(a). If the identity of the patient cannot be established or the patient's legally authorized representative cannot be contacted within two hours using the previously described algorithm(s), the investigator may initiate the process required for enrolling a patient in the PEG-SOD study where an exception to informed consent is necessary. The following procedures will be carried out:

(a) A nonparticipating physician will conduct a physical examination of the patient and review his/her medical records in order to determine the patient's eligibility to participate in the protocol. The nonparticipating physician will be a licensed ER physician who is trained and experienced in the management and treatment of severe head trauma.

(b) The nonparticipating physician will make an independent determination that the four conditions set out in 21 CFR 50.23(a) have been met. These conditions are as follows: (i) The human subject is confronted by a life-threatening situation necessitating the use of the test article; (ii) informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject; (iii) time is not sufficient to obtain consent from the subject's legal representative; and (iv) there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(c) The nonparticipating physician will certify the exception to informed consent is justified under 50.23(a), which will then be co-signed by the investigator. Copies of the certification will be maintained in the subject's medication order record, and in the investigator's study file. In addition, a copy of the certification will be submitted to the IRB within five work days following use of the test article.

Obtaining a Waiver of Informed Consent under 45 CFR 46.116(d). As per the provisions of the 12 August 1993 OPRR report on waiver of informed consent,[4] the IRB will document compliance with all four conditions specified in 45 CFR 46.116(d) as part of the protocol review record. These conditions are as follows: (i) the research involves no more than minimal risk to the subjects; (ii) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (iii) the research could not practicably be carried out without the waiver or alteration; and (iv) whenever appropriate, the subjects will be provided with additional pertinent information after participation. In contrast to the requirement of 21 CFR 50.23(a), it is not necessary for the investigator to provide certification of compliance to the IRB on an individual subject basis when a waiver of informed consent is used.

Continuing Efforts to Contact the Subject's Legal Representative after an Exception to Informed Consent Has Been Used. Following enrollment in the protocol after an exception to informed consent has been used, the investigator will continue to make a reasonable and conscientious effort to contact the legal representative of the subject and obtain written proxy consent for the subject's continued participation in the research. These efforts will include, as necessary, a daily calling campaign consisting of at least two calls during the day and at least one call after 8:00 p.m. until the representative is contacted, the subject regains competency, or the subject expires while on protocol. Local law enforcement officials will be used to help establish contact. All contact efforts will be documented in the medical record and a weekly report submitted to the IRB.

If the subject should die before contact is made, the investigator will notify the deceased's legally authorized representative as soon as possible. The representative will be provided with all of the information required by 21 CFR 50.25, including a description of the algorithm used to contact the representative and justification for enrolling the subject in the research without consent. The representative will be informed that he/she has the right to deny the investigator use of any research data collected on the subject.

Withdrawal of a Subject upon Refusal of the Representative to Consent to the Subject's Continued Participation in the Study. If a subject is enrolled in the study when an exemption to FDA informed consent requirements is used, the investigator will obtain proxy consent for continued participation of the subject in the study as soon as possible from the subject's legally authorized representative. If, however, the subject's legal representative refuses to provide consent for the subject's continued participation in the study, the patient will be removed from the study and the representative given the option to disallow use of any research data collected on the subject.

Discussion

The UNMC IRB noted that the FDA PEG-SOD guidelines reflected, in general, a number of the elements of the board's review of the PEG-SOD study and the specified conditions of approval described in our initial article. Perhaps of greatest interest, however, is the strong position that both FDA and OPRR took relative to use of a procedure referred to in the PEG-SOD protocol as "deferred consent." During the IRB's review of the protocol, there was vigorous objection to the entire concept of deferred consent as an oxymoron. One cannot consent to an intervention that has already been performed. FDA and OPRR also objected to the use of

deferred consent. FDA stated in the PEG-SOD guidelines, "The term does not occur in regulations of the Department of Health and Human Services or the Food and Drug Administration. It has been used in the past, however, to describe a procedure whereby subjects or representatives of subjects are informed, after the fact, that the subject participated, unknowingly, in a clinical investigation of an experimental drug product, and was administered a test article in the course of the clinical investigation. Subjects or their representatives are then asked to ratify that participation retroactively, and agree to continuing participation. Post hoc ratification is not true consent because the subject or representative has no means to prevent the administration of the test article, and cannot, therefore, meaningfully be said to have consented to its use." OPRR articulated a similar view by stating in its 12 August 1993 report, "Recently, we have become aware of the use of a consent procedure referred to as 'deferred consent' or 'ratification.' Informed consent procedures which provide for other than legally effective and prospectively obtained consent fail to constitute informed consent under the HHS Regulations for the Protection of Human Research Subjects. Similarly, the waiving of informed consent, using a method other than that requiring the IRB findings and IRB documentation specified at 45 CFR 46.116(c) or (d), is not in compliance with the regulations."

To our knowledge this is the first definitive position that either FDA or OPRR has taken on deferred consent, which has often been described in the literature. As we pointed out in our article on the IRB's review of the PEG-SOD study, many INDs approved by FDA have included a deferred consent procedure and FDA has a number of new drug applications (NDAs) on file that include data obtained on subjects where a deferred consent procedure was used. Thus, it would appear that it has been common practice in the past for investigators to utilize deferred consent and for IRBs to approve this consent procedure. The current FDA and HHS Regulations for the Protection of Human Research Subjects have been in effect since 1981 and it is, therefore, surprising that the issue of deferred consent in relation to the regulations has remained dormant until recently.

The IRB was very interested in the FDA's requirement in the PEG-SOD guidelines that directed the sponsor to develop an algorithm to be used by investigators to reach a consistent decision regarding an exception to and a waiver of informed consent. In our initial review of the PEG-SOD protocol we only required the investigator to make a reasonable attempt to contact the patient's legal representative before enrolling the subject in the protocol. The UNMC IRB failed, however, to ask for a detailed plan such as that now required by FDA. Certainly, the use of algorithms helps the investigator and the IRB to better protect the rights and welfare of incompetent subjects. In retrospect this IRB should have identified the need for an algorithm.

Now that the PEG-SOD study has created federal interest in the ethical and legal problems associated with ER research, it is our hope that FDA and OPRR will continue their joint efforts to find ways in which ER research involving acute trauma patients can be conducted either under the current regulations or under new regulations. While the UNMC PEG-SOD study guidelines discussed in this article should prove helpful to investigators and IRBs alike, it is obvious that federal regulators have not yet adequately addressed the ethical and legal issues that affect the ability of physicians to enroll incompetent patients without available representatives in ER research under current FDA/HHS regulations. Indeed, it should be pointed out that because the UNMC adopted the HHS regulations as a single standard, this limits our freedom to conduct ER research that is in our opinion medically and ethically justified but not approvable under 45 CFR 46. Shortly after HHS promulgated its regulations in 1981, Pattullo cautioned institutions to consider carefully the assurance they submit to HHS. Pattullo expressed the opinion that while the new regulations are sound in most respects they contain unnecessary protections that may inhibit a university's pursuit of free and responsible inquiry.[6] Levine agreed with Pattullo's advice and, in his editor's note, encouraged IRBs to "reserve the authority to develop rational institutional guidelines that IRB members can defend in their institutions and communities and that they impose indefensible rules only when explicitly required to do so by law."[6] While neither Pattullo nor Levine specifically addressed the issue of ER research during their discussion of assurances, the "PEG-SOD saga" offers support for the validity of their fear that well-intentioned federal regulations can unnecessarily impede worthwhile research.

In conclusion, we believe that ER research is of vital importance but must be conducted only under circumstances that offer subjects the prospect of an acceptable level of direct therapeutic benefit and that do not adversely affect the rights of the subjects. We trust that FDA and OPRR, in consultation with ER physicians and bioethicists, will ultimately provide IRBs with tangible and ethically defensible criteria that can be used to make judgments regarding the approvability of ER research protocols.

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ATTACHMENT C

Dr. Gary Briefel's Testimony

Deferred Consent: Use in Clinical Resuscitation Research

Deferred consent, a new approach to the requirement for informed consent in clinical research, was used in a randomized clinical trial of brain resuscitation after cardiac arrest. Because patients were comatose and therapy had to be initiated immediately, traditional prospective consent usually could not be obtained. Using the deferred consent mechanism, family members were contacted after the first dose of experimental drug or placebo was administered and asked to consent for continued study participation. The vast majority of families were satisfied with the deferred consent mechanism. Their main concerns were about the safety of the experimental drug and whether the active drug or placebo was given. The concepts of randomization, blinding, and placebo-treated controls were generally not well understood. Although our experiences confirmed the impracticality of attempting to obtain traditional prospective consent in clinical resuscitation research, deferred consent was found to be a reasonable solution. [Abramson NS, Safar P. Brain Resuscitation Clinical Trial II Study Group: Deferred consent: Use in clinical resuscitation research. Ann Emerg Med July 1990;19:781-784.]

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INTRODUCTION

Regulatory constraints on the conduct of clinical research have increased dramatically in recent years because of growing societal concern about ethical issues. One of the areas of greatest concern, the guarantee of patient rights and individual autonomy, was addressed by implementing the requirement to obtain informed consent. According to current Department of Health and Human Services regulations, informed consent must be obtained before conventional or experimental therapy may be administered to any patient involved in federally funded biomedical research.[1]

In previous papers[2,3] we have discussed the difficulties of obtaining informed consent in resuscitation research. Briefly, resuscitation research involves patients with acute, life-threatening conditions. If resuscitative therapy is to be beneficial in these emergency situations (eg, cardiac arrest), it must be administered during or very soon after the insult, before irreversible secondary changes occur. Patients are usually comatose when therapy is initiated and therefore cannot give informed consent. In such *emergency* situations, the physician has an obligation to do what is best for the patient and consent for treatment is not required.[4] However, this "emergency exception" may not apply to treatment determined by and administered as part of a research protocol.

Under state law, permission of the next of kin is ordinarily accepted as adequate consent for treatment of incompetent patients.[5] However, family members are often not immediately available in emergency situations. If present, they are likely to be in a state of emotional shock impeding their ability to comprehend the information provided or to make a rational decision.

Five years ago we adapted a "deferred consent" mechanism, as first discussed by Fost and Robertson,[6] in an attempt to solve the inherent conflict between regulatory constraints, ethical considerations, and the methodologic constraints of resuscitation research. We proposed that the use of deferred consent is appropriate in resuscitation research protocols involving all of the following conditions:[3] the patient is incompetent (co-

matosc); the experimental therapy must be administered immediately if it is to be beneficial; the experimental therapy does not pose meaningful additional risk to the patient; and the state of scientific knowledge is such that the investigator does not and cannot know whether standard or experimental therapy is better. The third and fourth conditions can be interpreted as requiring that the risk/benefit balance for study subjects cannot be less advantageous than if they were not in the clinical trial.[7]

This deferred consent approach was used in our randomized clinical trials of brain resuscitation after cardiac arrest.[8,9] It allowed initial treatment of patients in a carefully designed, institutional review board (IRB)-approved research protocol without obtaining prior informed consent. We now report on our experiences using this deferred consent mechanism.

METHODS

The Brain Resuscitation Clinical Trial II (1984-1989) was an international, collaborative, randomized clinical study of brain resuscitation after cardiac arrest. Twenty-four hospitals in eight countries participated in this double-blinded, placebo-controlled trial of experimental calcium entry blocker (lidoflazine) administration to comatose survivors of cardiac arrest.[7]

Individual consent forms for both prospective and deferred consent were developed at the University of Pittsburgh and approved by its Human Use Committee. These consent forms were distributed to all investigators and used as models. They were modified according to local hospital policies and community/national traditions and regulations. Study protocols, including the deferred consent mechanism, were reviewed and approved by each participating hospital's IRB.

To be eligible for the study, cardiac arrest patients had to remain in deep coma after spontaneous circulation was restored. Randomization and the first dose of experimental drug or placebo (three doses given within 24 hours) had to be initiated within 30 minutes of restoration of spontaneous circulation. Although investigators were free to obtain either traditional prospective consent or deferred consent, these methodologic constraints usually precluded the possibility of obtaining prospective consent.

Using the deferred consent mechanism, the patient's family was contacted to consent to continued participation in the study *after* the first dose of experimental drug or placebo was administered. This was almost always accomplished before the second dose was due eight hours later. Once family members were reached and the initial emotional reaction to learning of their relative's cardiac arrest subsided, the research protocol, including the need for randomization and double-blinding, was explained. At that time, they were provided with all the information that would have been supplied in order to obtain traditional prospective informed consent. They were also informed that the patient could be withdrawn from the study (so that all subsequent therapy would be nonexperimental) if the family so desired. They were reassured that no negative feelings would be engendered by such a withdrawal.

Family members were then requested to consent to continued participation in the research protocol and to sign the deferred consent form. In cases where family members could not be located, the attending physician (not associated with the study) was asked to sign the consent form as the patient's representative.

Study investigators completed a narrative report describing the process of obtaining deferred consent. Family reactions and questions, their decision, and any unusual circumstances were documented. These reports then were abstracted and analyzed by the study coordinator. Follow-up telephone discussions between the study coordinator and the hospital investigators amplified and clarified these written reports.

RESULTS

Prior to the start of the study, the IRBs of 18 American hospitals and eight European hospitals reviewed the use of deferred consent in this study. Of the 18 American institutions, 16 approved the deferred consent mechanism. Two approved only the use of traditional prospective consent, primarily because of concerns about risk of liability. Constrained to using only the prospective consent mechanism, these two investigators withdrew from the study because of low patient recruitment (they entered a combined total of three patients). All eight of the European institutions approved the use of the deferred consent mechanism.

Five hundred fifty-eight patients were entered into the study, 343 (61%) in the United States and 215 (39%) in Europe. Reports on the family reactions to the consent process were obtained for 266 (78%) of the American patients and 102 (47%) of the European patients (Table).

Prospective consent was attempted in only 28 cases. In this situation, families often felt pressured into making a decision before they were ready. Some wanted to consult with their own doctor. In one case, this resulted in a delay of the administration of the first experimental drug/placebo infusion. Prospective consent was refused once. In this case, the patient was a long-term survivor of our first brain resuscitation clinical trial (which tested high-dose thiopental loading in comatose cardiac arrest survivors). The patient's wife believed that they had been granted two and one-half additional years together and it was now "time for him to go."

The deferred consent mechanism was used in 531 (95%) of study patients. In 12 instances consent for continued participation was refused. In these cases, because of the patient's underlying medical condition, the family wished that further therapy be withheld. In one of these, an Israeli lawyer expressed fear that administration of the experimental drug might improve her father's grave condition just enough to prevent death, leaving him in a vegetative state.

In nine cases the patient died before the family could be contacted. In eight of these, a request to sign the consent form was not made, although families were told that the patient had been part of a randomized clinical trial. In the ninth case, the family signed the deferred consent form without expressing any concerns.

Consent was not requested in two other cases. In one of these, the wife had a myocardial infarction when told about her husband's cardiac arrest. In the other, there was underlying hostility toward the medical team, unrelated to the study.

TABLE. *Consent process in 558 resuscitation research patients**

	Deferred	Prospective
Consent requested	531	28
Consent not obtained		
Family refused	12	1
Patient died too early	9	–
Family not found	8	–
Not requested	2	–

*Individual reports obtained on 368 patients.

In eight cases family members could not be located. In seven of these, the attending physician [not associated with the study] signed the consent form. In one case the patient signed the form himself, after he awakened.

Six negative reactions to the use of deferred consent were documented. In three instances, families expressed concern that instead of dying their relative might survive, but in a vegetative state. This did happen in one case and the wife was angry, believing that administration of the experimental drug had caused "meaningless survival" rather than a "merciful death." One family was worried about the potential harmful effects of the experimental drug, and another was concerned that "even doctors know little about the experimental drug." Finally, in one instance, poor communication between the medical team and family members [thought to be related to racial tension] caused expressions of distrust and anger. This was resolved when more moderate family members arrived. In all of these, deferred consent was eventually granted by family members.

Often, relatives would delay making the consent decision until they could consult with other family members. Two families refused to make a decision until out of town relatives arrived. In one instance, they arrived barely in time to consent for the second dose of drug. One family wished to consult with their private physician. Despite repeated attempts, he could not be reached. Finally, with only ten minutes left before the second dose was due, they signed the consent form after consultation with the director of the ICU [not associated with the study]. Whether they felt coerced or reassured by this "objective" additional input is not known.

DISCUSSION

The concept of consent implies the possibility of refusal. Because consent cannot be granted for that which has already occurred, the term "deferred consent" is clearly a misnomer. Rather, this mechanism functions to assure that appropriate information is conveyed in a reasonable time frame and that family members have the opportunity to decide on *continued* participation in the research project.

Given the conditions of our study, ie, patients were comatose and the first dose of experimental drug/placebo had to be initiated within 30 minutes of restoration of spontaneous circulation, traditional prospective consent was usually impossible to obtain. However, families were generally satisfied with the "deferred consent" mechanism and expressed positive feelings about participating in the study. Being part of a National Institutes of Health-funded international clinical trial created feelings of reassurance that everything possible was being done. Most families expressed desires "to take any chance to save a loved one" or "to do whatever is best to help the patient." Many expressed desires "to help with research." A nurse who had previously taken care of several study patients readily granted deferred consent for her father's participation in the study.

Many families stated that trust in the medical staff influenced their decision. Some wished to be led through this difficult situation, expressing sentiments like "do whatever you think best," "you know more about this than we do," and "we know you'll do the best thing." Europeans seemed to be more trusting of physicians than Americans and less dependent on written documents. Commonly, they stated that they had no objections to the study but did not want to sign the consent form, explaining "it's for doctors to decide," "I don't want to be responsible," and "You only have to sign for bad things – like a bank loan." In general, Europeans [both institutions and individuals] were less concerned with "legalistic" issues.

Although concerns were often expressed about the safety of the experimental drug, few families requested detailed information regarding this or the study methodology. Even fewer understood the concepts of or need for randomization, blinding, or placebo controls. Many felt relieved that something was already being done and that their relative might get "special" treatment. Families often expressed a desire that the active drug, not the placebo, be given. Most understood that the initial dose had to be given immediately to be beneficial and that time did not allow for prior consent. Continued participation in the study was refused only when families thought, because of the patient's underlying state of health, that further lifesaving therapy should be withheld.

Individual reports on the consent process were not received for all study patients. However, all investigators confirmed that any negative or unusual family reactions were documented. Because investigators readily shared their "most interesting" consent experiences during discussions of this topic at annual study meetings, it seems unlikely that noteworthy family reactions were not reported. More importantly, however, the role of obtaining consent was not separated from that of assessing the consent process. Clearly, investigator bias may have affected the results of this "interview" research. Nonetheless, we believe that our results indicate general acceptance of this process by family and patients.

A decade [1979-89] of experience with the Brain Resuscitation Clinical Trials I and II confirms the impracticality of attempting to obtain traditional prospective consent in clinical resuscitation research. Although prospective consent for the use of experimental therapies might be obtained on already hospitalized patients at risk for a future catastrophic event, eg, cardiac arrest, this approach is clearly not feasible for the non-

hospitalized population. As the scope of emergency medical care broadens, time becomes an increasingly important factor and the difficulties of obtaining informed consent become more acute.

CONCLUSION

In our attempt to resolve the conflicts between regulatory constraints, ethical considerations, and necessary resuscitation research methodology, we have used a "deferred consent" mechanism. Although clearly a compromise, this appears to be a workable solution, striking a reasonable balance between patient rights and methodologic constraints of resuscitation research.

Alan Meisel, JD, and Bruce Miller, PhD, reviewed the manuscript and provided guidance and valuable suggestions. Jeanette McDew provided secretarial support.

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Written Testimony of Mark Todd, M.D.,Director Medical Affairs-Product Strategy, The Upjohn Company

Before the Subcommittee on Regulation, Business Opportunities & Technology, U.S. House of Representatives

May 23, 1994

My name is Wesley Mark Todd. I am a physician with specialty training in neurology. I have trained in clinical research and have been directly involved in various aspects of clinical research for more than 10 years. I have been a subject volunteer, investigator, medical monitor, member of an Institutional Review Board and director of a clinical investigation unit. Currently, I am Director, Medical Affairs-Product Strategy at The Upjohn Company. Upjohn is a worldwide, researched-based manufacturer of human health care products, animal health products, agronomic and vegetable seeds and specialty chemicals.

Upjohn was invited to testify today because the company is currently developing an experimental

emergency treatment called tirilazad mesylate. This drug is being tested in people who suffer subarachnoid hemorrhage, a type of stroke caused by a ruptured blood vessel and subsequent bleeding into the brain. It is being tested in people with ischemic strokes, which are caused by the blockage of an artery that supplies blood to the brain, resulting in the suffocation of brain tissue. And it is being tested in people who suffer head injury and spinal cord injury. All of these are devastating medical conditions with high rates of mortality and morbidity and with few or no current treatment options.

The purpose of my testimony is to elaborate on several key points that relate to the participation of people in biomedical research and to a pharmaceutical company's ability and responsibility to develop therapies that are significant advances against unmet or undermet medical needs.

The first point is that the autonomy and safety of volunteers and the integrity of the scientific

research are the most important aspects of Upjohn clinical trials.

Second, the development of effective medicines depends upon patients who volunteer for clinical studies.

Third, the development of life-saving medicines for some life-threatening medical conditions depends upon an exception from traditional prospective informed consent. Without such an exception important life-saving medicines cannot be developed as effectively and efficiently, and the availability of new treatments may be significantly delayed.

This issue is important to both emergency medical care--the routine treatment of life-threatening illnesses--and to the development of new medicines for emergency medical situations. In both cases, treatment may be administered to subjects who cannot give prospective informed consent. Without an ethical process to guide exception to informed consent, standard life-saving emergency care would be altered to the detriment of the

patient. And progress in emergency care would be slowed.

Before I elaborate on these statements, The Upjohn Company acknowledges that the participation of human volunteers in biomedical research poses complex ethical, social, legal and medical issues. As a result, the subject should be discussed openly and often and in forums where a diversity of non-scientists and scientists are represented. For this reason, the company appreciates the efforts of the chairman to arrange for a meaningful discussion and is pleased to present its views.

Upjohn values meaningful prospective informed consent as a foundation of ethical medical treatment and research. It is a goal toward which physicians and Upjohn continually strive. The company has developed Standard Operating Procedures for all Upjohn-sponsored clinical studies. These describe the policy and procedures related to informed consent. Upjohn's policies are based upon worldwide

standards for the conduct of human clinical trials. Upjohn also has developed specific procedures to ensure that each investigator complies with FDA regulations or the standards of other countries' national regulatory bodies.

The company's objective is to ensure that informed consent is a two-way conversation that respects the autonomy of an individual. This conversation between investigator and potential research subject makes clear to the volunteer that he or she is being asked to participate in an experiment. The experimental drug may prove beneficial to the patient, but the uncertainty of this is stated.

The conversation outlines the purpose of the study and the nature of all potential hazards. When hazards may not be known, that fact is made clear during the conversation as well as the fact that the individual may choose to withdraw from the experiment at any time.

The conversation includes information on the

design of the study and why it is designed in a particular way. For example, if the study is double-blinded and placebo-controlled, the volunteer is told what that does and does not mean.

In blinded, placebo-controlled studies of drugs for non-life-threatening diseases, volunteers in the comparator arm receive a placebo or, in some cases, an alternative therapy. Subjects in the experimental arm receive the experimental drug.

In blinded, placebo-controlled studies of drugs for life-threatening diseases, subjects in the comparator arm receive medically accepted standard therapy plus placebo while subjects in the experimental arm receive the medically accepted standard therapy with the experimental medicine added on.

A potential volunteer for a double-blinded, placebo-controlled study is told that this type of study is necessary to determine the effectiveness of an experimental drug. Double-blinded, placebo-controlled studies are the gold standard for the

determination of whether a drug works. The volunteer should also be informed of the probability of being randomized into a comparator arm of the experiment. The study may be attractive to the volunteer for the possibility of receiving an experimental therapy. The conversation should make clear that participation does not guarantee the volunteer will receive an experimental drug.

I have used the word "conversation" in order to stress that the investigator has an obligation to listen to the concerns of the volunteer and to encourage the volunteer to articulate his understanding of both the experiment and and his rights as an autonomous individual. The physician-investigator must probe the volunteer's understanding with questions and encourage the person to discuss any concerns.

It is clear from what I have said that meaningful prospective informed consent requires time and the ability to understand and communicate.

One of the issues germane to this hearing is under what circumstances and according to what parameters should exceptions to informed consent be granted. For example, what alternative procedure for prospective informed consent should be applied in an emergency room setting when a person is unconscious and the time for treatment is short?

On this issue, The Upjohn Company would make three statements. First, we acknowledge that the question of how to conduct research in emergency situations when patients cannot understand or communicate is one of the most challenging questions facing those interested in the ethics of clinical research.

Second, in some cases, exceptions to prospective informed consent should be made. These exceptions should be carefully considered and may be rare. But I must stress that a strong ethical, social and medical case can be made for exceptions to informed consent because the development of some potentially life-saving medicines depends upon such exceptions.

Third, in those cases where exceptions to prospective informed consent will be sought, a prescribed process should be followed prior to the commencement of the experiment.

Clinical investigators who write protocols--the blueprint of a clinical study--must evaluate and confirm the circumstances that require exception to informed consent. And they must formulate an ethical process to secure such exceptions. The protocol's alternative informed consent process must be reviewed by the FDA and by a diverse group of persons--scientists and non-scientists--known as the Institutional Review Board (IRB). I will say more on IRBs later. At this time, I stress that both the FDA and the IRB have the authority to reject, modify or approve the protocol and its informed consent procedures.

In the U.S., Upjohn clinical investigators rely upon FDA regulations that specify the conditions for valid exceptions to prospective informed consent. For research conducted outside the U.S., Upjohn

relies upon the standards of the national regulatory organization. Upjohn acknowledges the effort of the FDA on issues that affect the conduct of biomedical research. And Upjohn agrees with FDA on conditions for exception to informed consent specified in 21 CFR 50.23.

1. The study focuses on a life-threatening event.
2. The patient is unconscious.
3. Administration of the experimental medicine does not allow time for the subject to regain consciousness or for a family member to be contacted.
4. There is no alternative treatment that provides an equal or greater likelihood of saving the subject's life.

Upjohn also believes that the experimental medicine must have a favorable safety profile.

These facts characterize our studies of tirilazad mesylate in head injured individuals. Head injury is a life-threatening and seriously-debilitating medical condition for which no effective treatments exist.

Many head injured individuals arrive at the emergency department unconscious.

Continuing analysis of safety data shows tirilazad to be safe and well-tolerated.

Experimental evidence suggests that tirilazad interferes with a destructive biochemical process that occurs within the first several hours after a head injury. During these hours, this biochemically-induced secondary injury destroys additional vulnerable brain tissue. For this reason the head injury study protocol calls for administration of the first does of tirilazad within four hours after injury. This compressed time period for treatment is reduced by the time required for the subject to reach the emergency department, the time required to gather baseline information on the patient, and the time required to ensure the patient is a suitable candidate with no conditions that would limit his or her participation.

The short time period for drug administration, the safety profile of the drug and the subject's

impaired state of consciousness as a result of injury, together underscore the need for an exception to informed consent.

The decision to include an unconscious head injured patient in the tirilazad study is first sought from the patient's family. If a family member cannot be located, the decision to enroll the patient must involve a physician who is not participating in the head injury study. If the exception to informed consent is granted, the inclusion of the patient in the study is communicated to the patient's family immediately and to the IRB within five days. As soon as a family member is located, the informed consent conversation proceeds. The family member has the authority to decide if the patient continues in the study. If the subject regains the capability of giving informed consent during the course of treatment, the informed consent conversation occurs, and the subject may choose to continue or discontinue study treatment.

IRBs are a vital guarantee of the ethical conduct

of human research. The diverse membership of these bodies (as defined in federal regulations) ensures representation from both the scientific and the non-scientific communities. IRB members review the entire proposed study. They deliberate upon factors that make up the risk/benefit equation appropriate for the experiment. They review all elements of the experiment's informed consent process and have the authority to reject, modify or approve the process. No Upjohn clinical study will begin without review and approval from an IRB. The FDA oversees and inspects U.S. IRBs.

Upjohn believes that IRB review of biomedical research works with great efficiency and that it is a unique and effective system for evaluating the ethical issues of clinical research and for ensuring the autonomy and safety of human subjects.

I will conclude as I began, with the assertion that the issues raised by clinical research--especially research with patients unable to provide informed consent--are important and need to be discussed

often and openly.

On that thought I will quote a passage from the book, How We Die, by Doctor Sherwin Nuland. He writes, "In the United States and democratic countries in general, the importance of airing different viewpoints rests not in the probability that a stable consensus will ever be reached but in the recognition that it will not. It is by studying the shades of opinion expressed in such discussions that we become aware of considerations in decision-making that may never have weighed in our soul-searching."

There are few subjects more deserving of soul searching than the participation of vulnerable patients in clinical trials. Such searching and the movement toward a consensus that will be forever dynamic will aid the development of life-saving medicines for head injury and other debilitating medical conditions. Upjohn welcomes the reevaluation of medical policies in an effort to identify better procedures to ensure the appropriate

protection of the autonomy and safety of patients and to ensure the protection of the effective and efficient development of experimental, life-saving medicines. Thank you for inviting us to be part of this important discussion.

UNIVERSITY OF CALIFORNIA, LOS ANGELES

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Statement of

Don A. Rockwell, M.D.

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Before the House Subcommittee

on Regulation, Business Opportunities, and Technology

of the

Committee on Small Business

U.S. House of Representatives

May 23, 1994

My name is Don Rockwell, and I am submitting this testimony on behalf of the University of California Los Angeles ("UCLA").

I am the director of the UCLA Neuropsychiatric Hospital and have practiced psychiatry for the past 27 years. I have a particular interest in matters relating to research and informed consent, having served as chair of an Institutional Review Board ("IRB") at another major research institution, and having taught medical ethics to students of medicine.

The protection of human subjects in medical research is a crucial issue. I am pleased that the Subcommittee is addressing this area, since it is both complex and continually evolving. It merits an open and full discussion among researchers, patients, legislators and regulatory agencies. Working together, these groups can make further improvements in the protection of human subjects in research, while avoiding simplistic, "quick-fix" changes that could -- despite the best intentions -- ultimately set back the development of improved treatments for disease.

At UCLA, we have always understood that informed consent and the protection of human subjects do not constitute a static process. Rather, continual monitoring and improvement, incorporating both institutional oversight (such as UCLA's IRBs) and regulatory oversight (such as the federal Office for Protection from Research Risks ("OPRR") are needed. We are always interested in examining ways to enhance our protection of human subjects.

Over the past three years, a UCLA schizophrenia study has been under review by the federal Office for Protection from Research Risks (OPRR), which was investigating allegations regarding informed consent made by some family members of patients in the study. UCLA fully cooperated with the review. As a result of the OPRR review, UCLA is making several significant

changes in documenting its informed consent and review process, including establishing an independent Data and Safety Monitoring Board to oversee those studies in which the clinical researchers are also responsible for the clinical care of psychiatric study subjects, and augmenting the three non-UCLA members of the campus's medical IRB with one or more subject representatives, who would represent the research subject's perspective on studies involving subjects with severe psychiatric disorders.

Before going into detail about the UCLA schizophrenia study, it is my obligation to inform the Subcommittee that I am operating under a severe ethical and legal constraint that prevents me from providing the Subcommittee with the full details of individual patient care in the study. This constraint is extraordinarily frustrating for me, because it prevents the entire truth from coming out. Indeed, if this constraint was removed and I was able to describe to you the specifics of some individuals patient cases in the study, the picture would become abundantly clear -- and the Subcommittee would see that these outcomes were indeed not the result of a lack of documentation of informed consent or of the design of the UCLA study.

As physicians, we are under both an ethical and legal obligation to protect the confidentiality of a patient's medical record. We are not able to discuss the specifics of a patient's medical record without the permission of the patient. The patients and/or their families have so far refused to grant permission for UCLA to discuss their cases. As a result, they have essentially created a de facto gag order for UCLA, giving rise to a situation where the patients and families can give their version of what happened, but the UCLA doctors are not allowed the same freedom. This "unlevel playing field" has resulted in broad publication of many inaccuracies and misunderstandings about the UCLA study, without the opportunity for rebuttal.

I cannot adequately communicate to the Subcommittee how frustrating this situation has become for the UCLA clinicians and researchers involved in the study. These professors have devoted their lives to treating people with schizophrenia and other mental illnesses, and to developing improved treatments. Although they could easily clear up the erroneous accounts of patient care in their study and restore their own reputations if they would break their ethical and legal obligations to these patients, they have steadfastly refused to do so -- protecting the privacy of the very same people who have made these public allegations against them. It will only be in retrospect-- when these patient records are discussed in an open court of law -- that the whole truth will come out.

I would now like to address four questions about the UCLA schizophrenia study:

1. What was the purpose of the study?
2. How was the study conducted?
3. Did the study intentionally cause subjects to relapse? and
4. What were the findings of the federal Office for Protection from Research Risks review, and what is UCLA's response to the OPRR findings?

WHAT WAS THE PURPOSE OF THE UCLA SCHIZOPHRENIA STUDY?

At least 1.2 million Americans suffer from schizophrenia, yet there is a great deal about the early stages of the disease that is not known. Schizophrenia is a devastating disease not only to the patient, but to the patient's family, as well. It is usually recurrent, despite the best treatments available. People with schizophrenia often experience periods of severe hallucinations, delusions and loss of contact with reality.

A goal of the UCLA schizophrenia study, "Developmental Processes in Schizophrenic Disorders," is to improve diagnosis and treatment of schizophrenia by understanding more about the development of the disease and factors that may help predict its course in individuals. Better identification of factors that make some individuals more prone to schizophrenia and to schizophrenic relapse should help us develop preventive intervention strategies in the future. Around the country, most research to date has studied chronic, long-term schizophrenic patients, whose course of disease and need for medication are better understood. Relatively little is known about patients who recently had an initial psychotic episode.

In order to fully understand the UCLA study, it is absolutely essential to understand three important facts about schizophrenia and its treatment:

1. **Although there are many medications that are commonly prescribed to minimize the symptoms of schizophrenia, each of them has significant drawbacks that limit their effectiveness.**

All of the typical, commonly prescribed medications for schizophrenia have serious side-effects (including a potentially irreversible movement disorder called tardive dyskinesia) and common uncomfortable side-effects (muscular stiffness, dry mouth, sleepiness, etc.). As a result, many people in the early stages of schizophrenia refuse to take their medication or take themselves off medication against their doctors' advice.

2. **There is a wide variation among patients in their degree of recovery during the years after initial onset of schizophrenia. For patients who are doing well, it is not clear to**

physicians how long to continue ongoing outpatient medication, which involves further risk of serious side-effects.

Some patients do well during periods off medication, while others do not. Similarly, some patients do well on medication and others relapse despite being on medication.

3. Because of the above-mentioned problems with medication and because of the variability among patients, it is common clinical practice worldwide for doctors to give patients periods without medication during the initial years after the onset of schizophrenia.

These periods need to be closely monitored, since some patients do well without medication, while others do not.

Little is known about the factors that determine which patients will do well off medication and which will not. One of the specific goals of the UCLA study was to identify factors that predict the need for short-term outpatient medication versus long-term, continuous medication. This is a key issue in the treatment of the early stages of schizophrenia, as noted above.

The treatment protocol in the UCLA study was similar to what is done in everyday clinical practice with patients in the initial years after the onset of schizophrenia. The study was not designed to cause relapse, but to observe patients for periods on medication and off medication, since this is what typically occurs in community practice. None of the patients who participated in the study was deliberately allowed to experience a relapse. As in common clinical practice, the UCLA doctors would intervene by recommending medication and/or additional therapy if the

patient showed signs of a psychotic exacerbation, which involves less intense symptom changes than a relapse.

HOW WAS THE UCLA STUDY CONDUCTED?

The UCLA study consisted of three phases. Before entering each phase, the potential study subjects were presented with both written and oral information about the study. (I will discuss below some of the changes in this process we have made as a result of the OPRR review.) For Phase One, potential subjects signed written consent forms that explained the initial screening interview procedure, that allowed the researchers to contact the patients' significant others, and that explained the testing procedures of this phase, and the fact that medication and other treatment would be provided at an outpatient research program at UCLA. Additional details were described orally and any questions were answered. The nature of the study and associated treatment were also described to close family members, who signed a form consenting to their own participation in some study measures.

Over the course of the study, even before the OPRR review, the written consent information was refined at several points, as we gained more information on ways to enhance the informed consent process. For example, more details regarding the starting medication dosage were added.

In the first phase, patients with recent-onset schizophrenia (that is, with an initial schizophrenic episode within the past two years) were started on a dose of 12.5 mg Prolixin Decanoate every two weeks.

As in community practice, the dosage was a starting point, not an unchangeable dosage. It was later adjusted upward or downward if needed, depending on the patient's symptoms and the drug's side-effects. The 12.5 mg starting dosage was determined by a comprehensive review of the scientific literature regarding Prolixin Decanoate and recent-onset schizophrenia.

In Phase One, the patients were seen at least every two weeks in the UCLA Aftercare Program. Medication and symptoms were monitored by a psychiatrist. A case manager provided training in everyday living and coping skills, and also monitored symptoms. Close family members were invited to a family education program. Family members were also encouraged to contact the staff if they had any questions or concerns. The staff also worked to keep family members informed about treatment, unless patients exercised their right to restrict such information. Adult patients have the right to exclude family members from being involved in their care, if they wish, and some patients in the study exercised this right.

Following Phase One, those patients whose medications had been monitored for at least one year and who were clinically stable for at least three months were offered the opportunity to participate in Phase Two. Phase Two was designed to mimic the common medical practice in the community, which is to give recent-onset schizophrenia patients trial periods off medication to determine if they can continue to do well without the medication. In Phase Two, study participants continued to be monitored in the UCLA Aftercare Program at least every two weeks, but had a12-week period on medication followed by a 12-week period on a placebo, or vice versa. In addition, close family members were encouraged to call the staff if they noticed any change in the patient's symptoms. More frequent visits to the Aftercare Program were recommended as clinically indicated. If patients did not show significant symptoms during this

period, they were offered the opportunity to try a longer period without medication, to determine whether they would continue to do well without continuous medication.

During Phase Two, the researchers monitored the patients for any signs of exacerbation or relapse. In fact, in Phase Two the researchers used more sensitive procedures than standard medical practice to determine at the earliest possible point if someone was experiencing a psychotic exacerbation.

Following Phase Two, patients could continue to receive treatment at the UCLA Aftercare Program, where they can be monitored and their medication is given as needed.

DID THE STUDY INTENTIONALLY CAUSE SUBJECTS TO RELAPSE?

Unfortunately, relapse among patients with schizophrenia is common, even with medication. None of the patients who participated in the UCLA study was deliberately allowed to relapse. As occurs in community practice, some of the study subjects did experience a relapse. The rate of relapse in Phase One of the UCLA study was 18 percent for a one year period, which is in the low end of the national average yearly relapse rate of 15 - 35 percent for schizophrenic patients on medication. Thus, in the UCLA study, patients off medication relapsed, and patients on medication relapsed. In its review of the study, the OPRR report found "no demonstrable basis for rejecting the UCLA IRB's determination that the methodological design of the Schizophrenic Disorders research is scientifically and ethically justifiable." (OPRR Report, p. 17 (May 11, 1994)) I have also attached a memorandum to OPRR from Dr. Frederick Goodwin,

former director of the National Institute of Mental Health, that confirms this point. Dr. Goodwin's memorandum is included in the OPRR report as Attachment G.

If those who are making the allegations would permit us to discuss their individual cases, it would be clear to the Subcommittee that it was not the study design nor the UCLA researchers that caused the subjects' relapses.

Some of the critics of this study have confused the design of the study with a secondary retrospective analysis published by Subotnik & Nuechterlein in The Journal of Abnormal Psychology (1988) that used different definitions of relapse. The two are completely distinct. In the study currently in question, treatment decisions were based upon observations of clinically significant symptoms of psychosis. The 1988 analysis, on the other hand, retrospectively applied a different set of definitions which were unrelated to any medication decisions made for patients in the study. Thus, it is incorrect to infer that the researchers used the 1988 article's definitions in treatment decisions.

A crucial point that has often been overlooked is the "clinical override" aspect of the study. At any point in the study, the researchers could (and in fact did) override the study criteria to provide medication or other treatment if needed by the patient. The patient's best interest always came first. Some patients in the UCLA study refused to go back on medication. When that happened, UCLA staff worked with the patient, and, as appropriate, close family members and others to urge the patient to resume medication. However, a physician cannot force adult patients to take or resume medication against their will, without a court proceeding.

As part of the OPRR review, UCLA provided detailed documentation regarding the researchers' adjustment of medications for patient participants to ensure that patient treatment was clinically appropriate. As noted below, the OPRR report found no evidence that the clinical treatment of the subjects in the study failed to adhere to currently accepted clinical standards.

WHAT WERE THE FINDINGS OF THE OPRR REVIEW, AND WHAT IS UCLA'S RESPONSE TO THESE FINDINGS?

The OPRR review found several areas of the informed consent documentation that were insufficient, and as a result we have already made the necessary changes. It is important to note that these were not the first improvements UCLA has made to its informed consent documents in this study. The informed consent documents in this study were regularly reviewed both by the UCLA medical IRB and by outside reviewers from the National Institute of Mental Health, and had been enhanced at several points during the course of the study. In fact, improvements in the informed consent process were made both before and during the OPRR review, demonstrating that informed consent is indeed an evolving process.

The OPRR report found "no demonstrable basis for rejecting the UCLA IRB's determination that the design of the Schizophrenic Disorders research is scientifically and ethically justifiable." The OPRR report also found "no evidence that the clinical treatment of Subjects 'A' and 'B' during their involvement in the Schizophrenic Disorders research failed to adhere to currently accepted clinical standards." (OPRR Report, pp. 17, 19 (May 11, 1994))

The changes required by OPRR included: adding information in the written informed consent documents that had been previously presented orally to the study participants, and adding

additional information about the study procedures and risks. UCLA has implemented these changes.

The OPRR report also found that while corrected or nonchronological entries in some study records did not reveal evidence of risk or harm to study subjects, certain recordkeeping practices (e.g., for correcting errors made in transcribing data) were unsatisfactory. The UCLA researchers have taken steps to assure that their staff understand the proper procedures for correcting errors in transcribing data.

The OPRR report also requires UCLA to place these schizophrenia research protocols under Single Project Assurances, and OPRR has conditioned the renewal of UCLA's Multiple Project Assurance on our timely submission of additional statistical data. The Single Project Assurances are already in place, and we are moving forward with the collection of the required information.

As noted above, as a result of the OPRR report, UCLA will add one or more "subject representatives" to its committee that reviews certain studies involving subjects with severe psychiatric disorders. We are currently seeking advice from a variety of sources, including patient-advocacy groups, to assist us in identifying these representatives. These subject representatives will augment the three non-UCLA members of the campus's medical IRB.

UCLA will also establish an independent Data and Safety Monitoring Board to oversee those studies involving subjects with severe psychiatric disorders in which the clinical researchers are also responsible for the clinical care of the study subjects.

The three-year OPRR review and report identified some areas in the UCLA study that needed to be enhanced, as well as those areas where the allegations by the complainants were not supported by the facts. UCLA shares OPRR's commitment to ensuring that people participating in research studies are properly informed about risks, and we are committed to minimizing those risks.

I would now like to turn to the Subcommittee's questions regarding the structure and functioning of the UCLA IRB. At UCLA, our IRBs are called "Human Subject Protection Committees." For consistency, I shall refer to our committees as "IRBs." There are two IRBs at UCLA -- one for medical research, and another for non-medical research.

The purpose of UCLA's IRBs is to protect the rights and welfare of human subjects who participate in research. To carry out this responsibility, our IRBs review each research project, identifying and resolving issues related to the use of human subjects. This review is guided by policies and procedures developed and refined over a very long period of time and based on Federal regulations, state law, and university policies. All research on human subjects at UCLA must be approved by an IRB.

UCLA's IRB for medical research is currently composed of twelve faculty members, two nurses, two pharmacists, and three public members that represent the community at large. The Committee meets on a weekly basis, reviewing an average of seven new studies at each meeting. Although primary and secondary readers are assigned to each study and lead the discussion, every member is expected to read each protocol and to participate in the discussion. For each research project, the risks and benefits, the rights of the subjects, confidentiality, and other issues are addressed. Particular attention is paid to the informed consent forms and written answers

provided by investigators to an established series of questions, as well as the text of the research project itself. The frequent result of this review is a letter to the investigator recommending changes in the research protocol and/or the informed consent forms, or for clarification of matters related to the research. If the requested changes are adopted by the investigator, and the clarifications are satisfactory, the Chair is authorized to approve the project. In many cases, however, the amended protocol must be resubmitted for review by the full IRB prior to final approval. In some cases, investigators are asked to appear before the IRB to answer questions regarding details of the study.

For the typical research project involving human subjects, the subjects are competent and are able to evaluate the research procedures and the possible associated risks. They are also given the time to reflect upon the project, to ask questions, and to discuss matters with the investigators. This is the foundation of informed consent. The IRB considers informed consent to be more than the consent document; it is a continuing process, a dialogue with the subject. It begins when researchers review the information on the consent form to assure that the subject understands the information, and it continues throughout the subject's participation in the research, as new information becomes available and as the subject has questions, for example, about possible adverse effects.

We continue to welcome suggestions and recommendations as the understanding of the protection of human subjects in research continues to evolve. We are particularly mindful of the ethical issues surrounding the participation of subjects in psychiatric studies. It may now be time for the nation to revisit the ethical guidelines articulated in 1982 by the President's Commission for the Study of Ethical Problems in Medicine, Biochemical and Biobehavioral

Research. At UCLA, we are deeply committed to participating in the national discussion of these important issues.

US House of Representatives
Committee on Small Business
Subcommittee on Regulation, Business Opportunities
and Technology
Hon. Ron Wyden, Chairman

HEARING ON INFORMED CONSENT
May 23, 1994

TESTIMONY OF NORMAN FOST MD MPH
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Mr. Wyden, thank you very much for the opportunity to speak today. I am Professor of Pediatrics and Director of the Program in Medical Ethics at the University of Wisconsin. I am past Chairman of the American Academy of Pediatrics Committee on Bioethics. I am a practicing pediatrician and have been Chairman of the Institutional Review Board at the Univ of Wisconsin for 17 years. I have done clinical research on the issue of informed consent itself, and published articles on the subject of so-called "deferred consent." I have also been consulted by the Food and Drug Administration on this issue.

It is widely acknowledged in United State ethics and law that a competent patient has a nearly absolute right to decide what shall be done to his or her body. The instrument through which this right is exercised is called informed consent. The question we are discussing today, as I understand it, is when, if ever is it ethically and legally appropriate to administer experimental treatment, particularly in emergency settings, without the consent of the patient. I have confronted this problem as a physician, and as Chairman of an Institutional Review Board which has reviewed studies in which the investigator claimed it was necessary to waive consent.

I would like to make 3 points in my brief comments: (1) there is widespread confusion as to what is legally and ethically

permitted under existing regulations; (2) this confusion is not good for the rights and interests of present or future patients; (3) it would be an error to try to resolve this problem by insisting on strict standards of informed consent in all clinical trials. *The process of obtaining informed consent is a means, not an end. Its purpose is to try to figure out what the patient wants. Strict standards of consent have interfered with the goal of treating patients in the way they want to be treated.*

First, let me talk of confusion. Whatever the rights and wrongs of the issue, there can be no dispute that the regulation of this practice is one of inconsistency and confusion. Investigators and institutional review boards are caught between two sets of regulations. On the one hand, the FDA (Food and Drug Administration) allows investigational treatments, without the consent of the patient or his/her representative, if the patient is confronted by a "life-threatening situation." In contrast, the regulations of the Dept of Health and Human Services (HHS), add a further restriction: investigational treatments without consent cannot be of more than minimal risk. Minimal risk means that "the probability and magnitude of harm or discomfort ... are not greater ... than those ordinarily encountered in daily life or during the performance of routine physical or psychological tests." To make it more confusing, the FDA statutory language has different standards for drugs and devices.

(I will refer to the HHS regulations as the NIH regulations, since they are administered by the Office of Protection from Research Risks at the National Institutes of Health.)

This confusion results in inconsistency, paralysis, and stretching of the term "minimal risk" beyond recognition. Let me be specific. There are new drugs which offer great promise in preventing the devastating brain damage that commonly results from a stroke or head injury. Such patients typically cannot consent, and a relative is often unavailable in the narrow window of time when such treatment is likely to be effective, perhaps within hours of the time of injury.

In some hospitals, studies have been approved by an IRB (Institutional Review Board) and implemented, without the consent of the patient or a relative. In other hospitals, such studies have been prohibited. In some cases, the IRB believes the study is ethically and legally justified, but stalls, or defers the proposal, because of a fear of punishment from the Office of Protection from Research Risks if it guesses wrong on whether the treatment really is of "minimal risk."

There is a wide range of interpretations of "minimal risk." Some IRBs have labelled a non-therapeutic kidney biopsy as "minimal risk." I can assure you, based on personal information, that the

writers of the regulations did not have this in mind when the term was first coined by the National Commission for the Protection of Human Subject in Research.

Regardless of whether one thinks the FDA or the NIH standard is the correct one, they are very different standards and the differences have led to confusion and frustration. The paralysis that results is not just a problem for the advancement of science and the interests of future patients, or the interests of manufacturers, though it is a serious problem for those interests. *The paralysis is a problem for present patients, many of whom would want experimental treatments, even though neither they or their relatives would be able to consent.*

Let me turn to the role of so-called informed consent as a gatekeeping mechanism in deciding whether experimental treatments should be used on incompetent patients. Some have suggested that it is morally and legally reprehensible that treatments of uncertain benefits and risks can be administered without consent. I disagree.

It should be obvious that the informed consent of the patient is not a necessary condition for providing standard treatments. Even when the patient is competent, it is widely acknowledged that what we call informed consent is often an "elaborate ritual,"

with many patients understanding little and not truly consenting. When the patient is incompetent, whether due to age or mental defect or acute illness, it is not in the patient's interest to insist that he/she consent before providing treatment. We allow others, typically next of kin, to provide permission for treatment.

You should realize that the vast majority of drugs and devices we use on children are experimental, in the sense that they have never been tested for safety or efficacy in the age groups in which they have been used. The same could be said with regard to treatment of women, particularly pregnant women. Many of these so-called standard treatments are far more risky than the investigational materials I was referring to earlier. The fact that treatment is standard, in the sense of being widely used and accepted, is no assurance that it is safe or effective or that it is in the interest of the patient.

This permission from relatives, while it provides legal authorization to proceed, is not consent of the patient. Ideally, it is another person's best guess as to what the patient would choose if he/she were competent. Sometimes this person misrepresents the patient, through ignorance or because of conflicts of interest.

Mr Chairman, I believe the central ethical point is this: consent is a means, not an end. The end which it serves is the patient's interest, ideally as defined by that patient. We do not serve the interests of patients by insisting on informed consent from the patient. While next of kin are generally excellent candidates for representing the patient's interests, they are not the only candidates. When next of kin are not available, and the only available effective treatment is experimental treatment, it is not always in the patient's interest or consistent with patient wishes to refrain from using that treatment just because a relative is unavailable.

To prohibit the use of experimental treatment when neither the patient or a close relative can consent, would be to act in a way that is contrary to the interests and desires of many patients and their relatives. In one large study involving experimental treatment given in an emergency setting without consent from the patient or a relative, over 95% of the relatives later said they were appreciative that the treatment was begun. Had it not been possible to waive consent in that study, the result would have been a course of action opposite to what the relatives would have wanted. This would have violated the purpose which informed consent is designed to achieve.

It is urgent that this confusion be resolved in a way that

protects the interests of patients. Because of transgressions by researchers in the past, I think it is appropriate that safeguards for patients in the experimental setting be especially strict, particularly when it is claimed that consent from the patient or a relative must be waived. I would like to offer suggestions for additional safeguard, supplementing the existing protection offered by the multiple levels of peer review, IRB review, and review and exposure from publications. These suggestions ar explained in more detail in attached publications.

First, studies in which waiver of consent is considered essential should be reviewed by what I call a "surrogate panel" of patients or relatives. These are individuals who will not be actual subjects, but who are familiar with the disorder being studied. These panels, or focus groups if you will, have been remarkably helpful in advising investigators and IRBs as to the likely wishes of actual patients.

Second, studies in which consent is waived should be reviewed more frequently than others, including an assessment of the patient's or relatives response when they have been informed after the fact that experimental treatment has been started. If objections appear, the IRB should be able to stop the study.

Finally, the Director of NIH or the Secretary of DHHS have the

authority under the regulations to conduct an independent review of such proposals before they can begin. This review could be delegated to an Ethics Advisory Board, though I would worry about the delays in relying on such a Board, even were it to be created.

In summary, it is not in the interest of present or future patients to be excluded from promising investigational drugs and devices simply because they cannot consent and a relative is unavailable. Such an exclusion would violate the purpose of informed consent, which is to do what the patient would want, as best we can determine that.

Waiver of consent calls for especially strict safeguards, to reduce the risks that sometimes result from an overzealous investigator.

In my opinion, the inconsistency between the FDA and NIH regulations is urgently in need of repair. There are many patients with possibly treatable injuries who will die or become disabled otherwise, which is not in their interests as they would define them.

Thank you again for the opportunity to speak today.

ETHICS IN EMERGENCY MEDICINE

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PART 3

Human Subjects in Cardiopulmonary Resuscitation Research

NORMAN C. FOST, M.D., M.P.H.

Case

Researchers have shown, in an animal model, that alterations in the technique of cardiopulmonary resuscitation improve blood flow to vital organs and increase survival of animals in cardiac arrest. The investigators would like to determine whether this technique will have similar effects on humans. The hospital Institutional Review Board (IRB) (Human Subjects Committee), using National Institutes of Health (NIH) guidelines, rejects the investigator's proposal because of the impossibility of obtaining the patient's informed consent. Does this mean that the research can never proceed and that lives will be lost because this potentially valuable medical procedure cannot be used on humans? What guidelines could investigators and IRBs use in judging these research projects?

Commentary

This case demonstrates how devotion to the principle of informed consent can be excessive, in the sense of being contrary to the interests of identifiable patients, as well as certain classes of patients and society as a whole. I will argue, first, that informed consent from human subjects of research is neither a necessary nor a sufficient criterion for conducting such research; second, that the IRB has seriously misunderstood the federal rules on this subject; and third, that the IRB suggest guidelines for reviewing this project and others which raise similar issues.

CONSENT SHOULD NOT BE A NECESSARY CONDITION FOR RESEARCH

The idea and practice of free and informed consent is intended to serve two important ethical functions: first, to protect patients from harm, and second, to respect autonomy by allowing patients to make choices based on their own values. It is important to remember that the *practice* is only a means, not an end. If it fails to achieve the end or interferes with such achievement, it should be reconsidered or modified.

While the Nuremberg Code (1) insisted on consent from the actual subject of research, subsequent analysis and rules have recognized the desirability of a less rigid position. In the case of therapeutic research on incompetent patients, particularly for diseases which have no effective treatment but for which a new treatment offers reasonable promise, a strict requirement for consent may be contrary to the patient's physical well-being (that is, may not protect him), and contrary to his personal values.

Consider, for example, the first application of external cardiac massage during a human cardiac arrest (21). Prior to the development of cardiopulmonary resuscitation (CPR), a diagnosis of cardiac arrest was tantamount to pronouncing death (5, 6). The most widely attempted remedy was to incise the chest, under nonsterile conditions, and squeeze the heart directly. The benefit of this procedure was remote, and the cost high in terms of distress to onlookers and those concerned with "death with dignity." Assuming the patient had an otherwise good prognosis and wanted to go on living, external cardiac massage would have a favorable benefit-risk ratio. For many patients, a strict requirement for consent would not have offered "protection" in the sense of preventing injury and maximizing health and would not have been consistent with their most strongly held values.

The conflict between consent, on the one hand, and protection and autonomy, on the other, arises in other settings besides the emergency room. A strict requirement for informed consent from research subjects would prohibit therapeutic research on children and the chronically mentally retarded. Diseases which affect those classes exclusively, such as disorders of prematurity and metabolic diseases which cause death in childhood, would remain therapeutic orphans. Such a policy would not protect such persons from harm. Whether it would respect autonomy is somewhat more complicated and requires a brief consideration of the justification for nonexperimental therapeutic interventions on incompetent patients.

No one would push the concept of consent so far as to require consent from an incompetent patient for a treatment of proven benefit, with minimal risk, in a clinical situation where nontreatment is likely to cause serious harm, for example, an appendectomy for appendicitis in a three-year-old. The obvious reason is that the protection function would not be well-served by such a requirement. But protection alone is not sufficient to justify intervention, since reasonable people disagree on the relative value of treatment versus nontreatment. A policy of allowing Jehovah's Witnesses, for example, to refuse lifesaving transfusions does not, from the perspective of the majority, seem to offer protection, but we regularly allow such refusals because the respect for autonomy is considered more important. But how is the autonomy of an incompetent to be respected?

In my view, it makes little sense to talk about the autonomy of an incompetent patient, particularly if the patient has always been incompetent to a degree that his wishes are unknown. A newborn can be autonomous, in the sense of acting on his own, but he will die without proper care, an outcome which will usually seem inconsistent with respecting him as a person. The closest we can come to what is at the root of autonomy, when an incompetent patient is involved, is to resort to a notion of substituted judgment: that is, to ask, "What would the patient likely say if fully informed and competent to make an assessment?" The answer would include consideration of the patient's unique circumstances, including the prospects of continuing life in an incompetent state. It might be, for example, that a vegetatively retarded person would refuse a treatment which would be accepted by most persons of normal intelligence, because the benefit of continued existence is so small. Therapeutic interventions without consent, according to this view, can be perceived as consistent with respect for the person, if not autonomy, if there is a supportable argument that treatment is what the patient would likely want if fully informed and free to choose. Similarly, therapeutic research in some situations can be justified if there are data to support the claim that the patient almost surely would have consented if competent to do so.

This view of permitting interventions on incompetent subjects without their consent still recognizes two ethically important objectives: first, to protect the patient from clear harms (that is, intrusions which would violate almost anyone's notion of protection), and second, to make the best estimate of what the patient would want, given his idiosyncratic condition and future prospects.

In summary, consent from the patient should not be a necessary condition for therapeutic interventions on incompetent subjects. The same arguments that justify interventions of proven benefits and risks would justify some experimental interventions. Proxy decisions in both cases require attention to the conditions for legitimate or ideal proxy decision making. Since the benefits and risks of experimental intrusions are less clear than the benefits and risks of standard treatment, the likelihood of consent is generally less, and the procedural requirements for proxy decision making should be more strict.

CONSENT IS NOT A SUFFICIENT CONDITION FOR RESEARCH ON HUMAN SUBJECTS

I have argued that consent is not necessary for therapeutic research on incompetent subjects. I would also make the point that it is not a sufficient reason for doing research on a competent patient. The case under discussion does not involve competent subjects who might consent, so this argument will not be presented in detail. I only present it as further argument for avoiding a slavish devotion to consent as the critical issue in research.

Consent alone would not justify interventions which might be outrageous on other grounds. Consider, for example, experiments which might be illegal, such as those conducted by unauthorized persons, or using illegally obtained or unauthorized materials, or which violate criminal laws, such as those prohibiting murder or mayhem. There are sufficient public policy interests in such prohibitions as to allow, at least, a balancing of public interests against the interest of a subject to consent to anything he wishes. Insofar as there is no fundamental right to experimental treatment, the patient's right to consent to this treatment would be less than his right to consent to standard treatment.

One could also argue that the protection and autonomy functions do not call for an absolute dependence on consent as the justification for research. The reality of consent is that it often does not protect patients well (7). For the same reasons, it does not maximize autonomy, because the misguided patient may make decisions which are contrary to his chosen ends. Consider, for example, the competent patient who, because of trust in the therapist, consents to quack cancer therapy but who insists his primary value is to live as long as possible. Assuming there is a known effective and safe cure for the condition, allowing consent alone to determine the course of treatment would not only fail to protect the patient from harm but would also thwart the attainment of his most strongly held goals.

FEDERAL RULES DO NOT REQUIRE CONSENT

The case report does not mention which section of the "NIH guidelines" led the IRB to deny approval, based on the failure to obtain consent. Assuming the IRB is relying on the Department of Health and Human Services rules which govern NIH-funded research (8), it is difficult to know what section they think prohibits this study.

The regulations clearly allow for therapeutic research from incompetent subjects (9), anticipating studies in which consent cannot be obtained from the patient (10–12). It is possible that the IRB misconstrued this as nontherapeutic research, but that would seem to have been an error, given the statement that the investigators wish to determine whether the technique will increase survival.

While there may be other ethical and or legal grounds for disapproving the research, the inability to obtain consent from the subjects does not seem to be a violation, per se, of federal rules.

GUIDELINES FOR CPR RESEARCH

Based on the discussion above, it should be clear that therapeutic research on human subjects who cannot consent should be ethically warranted in some circumstances. Emergencies constitute one example in which consent often cannot be obtained. The ethical bases for approving such research are: (a) failure to do so would, in some cases, not protect the health needs of potential patient-subjects; and (b) failure to do so would be to act contrary to the wishes and values of some patients and thereby fail to respect them as persons, in the same sense as denying standard treatment would constitute such a failure. I would not appeal to societal interests in allowing such research or agree with the claim that such patients have a duty to participate in such research (13), although one could *imagine* a national crisis in which the social utility of doing such a project would be so great that such considerations would be relevant. The federal rules allow for even *nontherapeutic* research in such a crisis, with special procedural rules, including review at a national level.

Because it is preferable for new ideas to be tried on persons with clear ability to consent, research on the incompetent patient should be considered only after initial studies on competent patients justify expanding the study population. It is not clear from the information provided whether or why the study was not initially tried on competent patients. For example, the modality being studied (a drug? body position? tourniquets?) could be tried in other clinical settings where competent patients could be invited to participate. Patients could be recruited from a class at risk for cardiac arrest, prior to becoming incompetent, such as patients about to undergo heart surgery with high risk of postoperative cardiac arrest. Assuming such options were not available, it should still be possible to do the research on incompetent patients, assuming the following conditions are met:

1. The person's wishes, if known, prior to becoming incompetent should be respected. This would include casual conversations with trusted relatives or a personal physician. It would not require a formal, informed declaration.
2. The animal data are impressive to persons competent to review it, so that the prospects for human success are reasonable. This should include, for example, publication in a reputable journal or expert opinion in some other form.
3. It is not possible to study the intervention in competent patients, or there is some compelling ethical argument for not doing so.
4. Rather than conducting the study in the emergency department, it should be done on patients already hospitalized. The reasons for this are that such patients and their families will be better known to the medical staff, and their values and wishes can be more reasonably assessed, than will patients in the emergency department who are more likely to be strangers. In addition, the ethical questions surrounding

the decision of whether even to proceed with CPR will be more informed in the inpatient setting. I assume this requirement will not substantially reduce the opportunity to enroll patients, given the high rate of cardiac arrest in a large hospital.

5. The procedures for proxy consent should make a reasonable attempt to emulate the criteria for an "ideal proxy" (14). This could include convening of a surrogate panel (15) made up of persons who approximate the prospective subjects in pertinent demographic and psychosocial characteristics.
6. Assuming the surrogate group approves the research, there should still be an effort to inform and, within reason, to ask consent of the next of kin who are available at the time of the CPR. The reason for this is that close relatives are more likely to know the patient's wishes than are others available at the time the decision must be made. Even though such consent would not be highly informed, such wishes should be respected.
7. Notwithstanding the apparent misinterpretation of federal rules, the approval of the IRB should obviously still be required, including appeal processes within the institution or to NIH.

NOTES

1. See the Nuremberg Code, reprinted in Section 3, p. 254.
2. The central component of cardiopulmonary resuscitation—external cardiac massage—was described in the 19th Century (Ref. 3) and actually rediscovered and developed in the 1950's by Koeuwenhoven and his associates after extensive animal research (Ref. 4). The example, therefore, is partly hypothetical.
3. Niehaus (1869), as quoted in Zesas, D. C. "Uber massage des freigelegten herzen beim chloroformkollaps." *Zentralblatt fur Chirurgie* 30:388, 1903.
4. Jude, J. B., Kouwenhoven, W. B., and Knickerbocker, G. G. "Cardiac arrest: report of application of external cardiac massage on 118 patients." *Journal of the American Medical Association* 178:1063, 1961.
5. Now, according to Nadas (Ref. 6), it is simply "the most serious arrythmia imaginable."
6. Nadas, A. S. *Pediatric Cardiology*, 2nd ed. Philadelphia: W. B. Saunders, 1964.
7. Ingelfinger, F. J. "Informed (but uneducated) consent." *New England Journal of Medicine* 287:465–466, 1972.
8. See the Regulations of the Department of Health and Human Services on the Protection of Human Subjects, reprinted in Section 3.
9. Regulations of the Department of Health and Human Services on the Protection of Human Subjects, 45 CFR 46. 116 General requirements for informed consent. 45 CFR 46, Subpart D: Additional protections for children involved as research subjects (1983).
10. By "therapeutic research" I mean research which, in the investigator's mind and the opinion of informed others, has a reasonable likelihood of benefiting the subject. The question of whether so-called therapeutic trials *really* are in the interest of subjects is beyond the scope of this commentary (Refs. 11 and 12). I assume that the proposed study is a Phase I–II trial and that competent reviewers believe there is reasonable likelihood that subjects who receive the experimental treatment will be better off than those who receive standard treatment.
11. Fried, C. *Medical Experimentation: Personal Integrity and Social Policy*. New York: American Elsevier, 1974.
12. Wilder, D. I. "Ethical considerations in randomized clinical trials." *Seminars in Oncology* 8(4):437–441, 1981.
13. McCormick, R. A. "Proxy consent in the experimentation situation." *Perspectives in Biology and Medicine* 18:2–20, 1974.
14. Post, N. "Ethical issues in the treatment of critically ill newborns." *Pediatric Annals* 10:383–89, 1981.
15. Post, N. "A surrogate system for informed consent." *Journal of the American Medical Association* 233:800–803, 1975.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

FOR RELEASE UPON DELIVERY

TESTIMONY OF

DR. GARY B. ELLIS

DIRECTOR, OFFICE OF PROTECTION FROM RESEARCH RISKS

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES,
AND TECHNOLOGY

COMMITTEE ON SMALL BUSINESS

UNITED STATES HOUSE OF REPRESENTATIVES

MAY 23, 1994

Mr. Chairman and Members of the Subcommittee:

I am Gary Ellis, Director of the Office for Protection from Research Risks (OPRR). With me today is Mr. F. William Dommel, Jr., OPRR Senior Policy Advisor. The Office for Protection from Research Risks, housed administratively and physically at the National Institutes of Health (NIH), is charged with implementing regulations regarding the Protection of Human Subjects (45 CFR Part 46) that have been promulgated by the entire Department of Health and Human Services (HHS). In doing so, OPRR oversees a well-developed, yet ever-evolving, system of protection of human research subjects. Thus, my testimony today describes the interests not just of NIH, but of the Department as a whole, in protecting human subjects in research--a responsibility of enormous weight.

Mr. Chairman, next Monday (May 30) will mark the twentieth anniversary of the formal promulgation on May 30, 1974 of our Department's regulations for Protection of Human Subjects in research. This enduring and vigorous system of protections is designed to preclude the very problems that we have gathered here today to discuss. Yet, it goes without saying that we are always interested in improving the system.

This system of protection of human subjects in research is based on a succession, or chain, of judgments made by people in the context of Federal regulations. People like you and me look at research protocols and weigh risks and potential benefits. There is no

computer program for this; there is no generic formula. This isn't done wholesale; it's done retail. One size doesn't fit all. This is custom work.

Who is involved in protecting human subjects? The architecture of the current system involves at least half a dozen levels of protection. First, and foremost, there is the interaction between the research volunteer and research investigator. This is where the informed consent process takes place. It must be an ongoing, dynamic process, as new information becomes available or is desired. The informed consent document, or form, is one component--the written component--of the informed consent process. I will describe the particulars of informed consent in a moment. There may also be other parties involved, such as nursing and scientific staff other than a physician. There may be a consent auditor or monitor, or an advocate for the research subject.

The Institutional Review Board, or "IRB," is, by Federal regulation, to be established at the local level and has a minimum of five people, including at least one scientist, one nonscientist, and one person not otherwise affiliated with that institution. The local IRB at the research site is the cornerstone of the American system of protection of human subjects. No human subjects research may be initiated, and no ongoing research may continue, in the absence of an IRB approval. Government agencies cannot provide funds for human subjects research unless an IRB approves the protocol for such studies.

IRB review is (i) prospective and (ii) continuing review of proposed research by a group of individuals with no formal interest in the research. It is a local review, by individuals who are in the best position to know the resources of the institution, the capabilities and reputations of the investigators and staff, and the prevailing values and ethics of the community and likely subject population.

Once research is underway, the IRB must conduct continuing review of the research, at intervals appropriate to the degree of risk--in any event, at least once per year. I will return to the responsibilities of the IRB in a moment.

An additional layer of review that is sometimes employed is an independent Data and Safety Monitoring Board, or "DSMB," appointed to oversee and to evaluate the research investigation. At periodic intervals during the course of an experiment, the Data and Safety Monitoring Board reviews the accumulated data and makes recommendations on the continuation, or modification, of the study. When a study is stopped prematurely because of a toxic effect or because a strong positive effect was seen, and it would be unethical to continue with some subjects not receiving the test article which has demonstrated benefit, it is likely due to the intervention of a Data and Safety Monitoring Board.

Downstream from the IRB are (i) the executive official of the research site, (ii) the scientific review group at the funding entity (e.g., one of the NIH Institutes or Centers, and

(iii) the executive official of that entity. Each has the authority to express concerns about human subjects issues. Exerting oversight of the whole process is OPRR.

While I've emphasized the multiple layers of protection inherent in this system, I know you are most concerned about the possibility that this system can somehow fail.

What is the possibility of a catastrophic failure in human judgment running through six or more layers? I would characterize that possibility as "slight."

To give you a sense of the kinds of problems that occur and actions taken to address them, I will relate brief accounts of some actions taken by OPRR in the past few months. In one instance, the concern was the proper explanation of risks in the informed consent process for a study involving schizophrenia. OPRR (i) rebuked the Institutional Review Board for poor oversight of the informed consent process, (ii) directed that the informed consent process be revised, and (iii) instituted close monitoring of the institution's human subjects activities. In a second instance, the concern was misuse of an expedited IRB review process. OPRR identified a failure of leadership within the Institutional Review Board, and the IRB Chairman subsequently resigned. At a third institution, the concern was whether or not the IRB was properly conducting the required continuing, annual review of research. The institution demonstrated to OPRR that some 2,000 research protocols involving human subjects had, indeed, received continuing review in accord with HHS regulations.

Institutional Review Boards

Let me turn briefly to the specific responsibilities of the Institutional Review Board. IRB review assures that:

- risks are minimized;
- risks are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- there is proper informed consent; and
- the rights and welfare of subjects are maintained in other ways as well. This is particularly important when subjects are likely to be vulnerable to coercion or undue influence.

What populations are judged to be vulnerable? IRBs watch out especially for research involving children, prisoners, pregnant women, individuals with mental disabilities, individuals who are economically disadvantaged, and individuals who are educationally disadvantaged.

The HHS regulations provide extra protection for vulnerable subjects in several ways. If an IRB regularly reviews research that involves a vulnerable category of subjects, consideration must be given to including as IRB members one or more individuals who are knowledgeable about, and experienced in working with, the vulnerable subjects. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, IRBs must see that additional safeguards are included in the study protocol. Specific, detailed

protections are actually written into HHS regulations pertaining to pregnant women, fetuses, human ova fertilized in vitro, prisoners, and children.

Assurance of Compliance with Human Subjects Regulations

The HHS regulations for Protection of Human Subjects are not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, this is a framework in which investigators, IRB members, and others can ensure that serious efforts have been made to protect the rights and welfare of research subjects.

OPRR oversees implementation of the regulations in all HHS facilities as well as domestic and foreign institutions or sites receiving HHS funds. OPRR requires that each HHS agency and extramural research institution that conducts research involving human subjects sets forth the procedures it will use to protect human subjects in a policy statement called an "Assurance" of compliance. At OPRR's discretion, institutions with a large volume of research and demonstrated expertise in human subjects protection may be granted a Multiple Project Assurance. A Multiple Project Assurance, as the term implies, is an institution's pledge of full human subject protections for multiple projects at the institution.

This Assurance statement is a formal, written commitment to: (i) widely held ethical principles; (ii) the HHS regulations for Protection of Human Subjects; and (iii) institutional

procedures adequate to safeguard the rights and welfare of human subjects. The terms of the institution's Assurance are negotiated with OPRR. The detailed, written Assurance statement becomes the instrument that OPRR uses to gauge an institution's compliance with human subject protections if there is a problem. It is interesting to note that the majority of reports of noncompliance received by OPRR come from institutions themselves.

The Department of Health and Human Services conducts or supports about $5 billion per year in biomedical research that involves human subjects at some 1,000 institutions (receiving approximately 15,000 awards) and many more affiliated performance sites. Of this human subjects research, the overwhelming majority is supported by NIH. OPRR responds to allegations of noncompliance from all sources (e.g., research subjects, institutions, media, Congress) and actively pursues investigations. OPRR is currently evaluating compliance in 63 cases at 49 institutions. Many of OPRR's compliance oversight activities involve some facet of the informed consent process.

Informed Consent

All present today know how integral--how crucial--the process of informed consent is. Many have a general picture of informed consent, and it is useful to add higher resolution to that picture of informed consent. Federal regulations specify eight required elements of informed consent:

1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

2) A description of any reasonably foreseeable risks or discomforts to the subjects.

3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

However, HHS regulations for Protection of Human Subjects provide an avenue, in certain narrow circumstances, for (i) a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or (ii) waiver of the requirement to obtain informed consent. The HHS regulations (45 CFR 46.116(d)) provide for waiver of the requirements to obtain informed consent when all four of the following circumstances pertain:

- the research involves no more than minimal risk to the subjects;
  ("Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(i)).)

- the waiver, or alteration, of consent will not adversely affect the rights and welfare of the subjects;

- the research could not practicably be carried out without the waiver or alteration; and

- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

IRBs are required to make and document these judgments.

Early last summer, in meetings between OPRR and Food and Drug Administration (FDA) staff, OPRR was alerted to a procedure termed by some as "deferred consent." The term "deferred consent" does not occur in the regulations of the Department of Health and Human Services, or in the regulations of the Food and Drug Administration. The term "deferred consent" has been used elsewhere, however, to describe a procedure whereby subjects, or representatives of subjects, are informed, after the fact, that the subject participated, unknowingly, in a clinical investigation of an experimental drug, and was administered the drug (or, perhaps, placebo) in the course of the clinical investigation.

Subjects, or their representatives, are then asked to ratify that participation retroactively, and to agree to continuing participation. This situation arises, for example, in the conduct of research on severe head trauma.

Post-hoc ratification is not true consent, because the subject (or representative) has no means to prevent the action, and cannot, therefore, meaningfully be said to have consented to the action.

Thus, procedures such as "deferred consent" that provide for other than legally effective and prospectively obtained consent fail to constitute informed consent under the HHS regulations for Protection of Human Subjects.

For institutions subject to the HHS regulations--and nearly all of the major U.S. research centers apply these rules to all biomedical and behavioral research--that does not mean that the HHS regulations present an absolute blockade to the conduct of, for example, traumatic head injury research. Consent from legally authorized representatives is authorized by the HHS regulations. When this is not possible, the regulatory avenue I described a moment ago--waiver of consent--is available in certain narrow circumstances.

The HHS regulations for Protection of Human Subjects provide one additional avenue for waiver of informed consent. In very rare circumstances, and unless otherwise required by law, the Secretary may waive the applicability of informed consent (or some or all of the other provisions of the regulations) to specific research activities or classes of research activities otherwise covered by the regulations.

Subsequent to the meetings with FDA alerting us to the problem, OPRR in the August 12, 1993 issuance of OPRR Reports delivered to 4,500 addressees worldwide, provided instruction from HHS on "Informed Consent--Legally Effective and Prospectively Obtained" (see attached). It specifically addressed the unacceptability of "deferred consent."

OPRR believes that the provisions for waiving informed consent, spelled out in the HHS regulations for Protection of Human Subjects, are workable. It should be clear, too, that the four regulatory criteria for waiving informed consent are quite restrictive. Waiver of informed consent is clearly not compatible, for example, with research involving greater than minimal risk to the subject.

It is important to note that nothing in the HHS regulations is intended to limit the authority of a physician to provide emergency medical *care* to a *patient*. HHS regulations for Protection of Human Subjects do not permit *research* activities to be started, even in an emergency, without prior IRB review and approval. If emergency *care* is initiated without prior IRB review and approval, the *patient* may not be considered to be a *research subject*. Such emergency *care* may not be claimed as *research*, nor may the outcome of such *care* be included in any report of a *research* activity.

The issue of circumstances under which specific research activities may go forward when prior informed consent cannot be obtained is one that needs further examination.

NIH and FDA are exploring ways to address this and other issues, and FDA, in its statement, will be further discussing the issues outstanding in this area.

The Federal Government actively conducts and supports biomedical and behavioral research involving human subjects. HHS regulations for Protection of Human Subjects describe certain ethical boundaries to that research. Is this position inimical to progress in certain, especially risky, areas of research? Consider the viewpoint of the eminent Yale University biocthicist Jay Katz: "I value respect for the dignity and integrity of man," said Professor Katz in U.S. Senate testimony 21 years ago, "even more than the advancement of science. For progress is an optional goal and we have much more to lose, as we have lost already, from the erosion of the moral values which inevitably follows any unauthorized invasion of man's mind and body."

OPRR shares with you, Mr. Chairman and Members of the Subcommittee, and with Professor Katz, a commitment to protect the rights and welfare of our fellow citizens who elect to volunteer for research studies, and who, in doing so, ultimately improve the lot of us all.

Thank you, Mr. Chairman. We are pleased to answer any questions about our system for safeguarding the rights and welfare of human research subjects.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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STATEMENT BY

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FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY SUBCOMMITTEE

COMMITTEE ON SMALL BUSINESS

UNITED STATES HOUSE OF REPRESENTATIVES

MAY 23, 1994

TO BE RELEASED ONLY UPON DELIVERY

Mr. Chairman and Members of the Subcommittee:

I am Mary Pendergast, Deputy Commissioner and Senior Advisor to the Commissioner of Food and Drugs, U.S. Food and Drug Administration (FDA). With me today are Dr. Robert Temple, Director of the Office of Drug Evaluation I, in FDA's Center for Drug Evaluation and Research, and Dr. Susan Alpert, Acting Director of the Office of Device Evaluation in FDA's Center for Devices and Radiological Health. We are pleased to be here today to discuss the agency's policy with respect to informed consent, particularly obtaining informed consent in clinical trials where patients are unable to give consent because they are unconscious. The issues involved are extremely important. The studies affected by this policy involve fatal diseases and conditions, often with no adequate treatment. The patients affected are an extremely vulnerable population entitled to maximum protection against abuse.

Of course, we share the view that all research must be conducted in an ethical manner. In the vast majority of FDA-regulated research, the ethical mandates requiring respect for the autonomy of patients and protection of patients with diminished capacity are satisfied by the statutory and regulatory requirement that the investigator obtain the consent of the patient who is going to participate in the clinical trial. If that patient cannot give consent because of age, loss of consciousness or other mental incapacity, the investigator must

obtain the consent of the patient's legally authorized representative.

What we are here to discuss today is that exceedingly small subset of research where it is impossible to obtain the informed consent of the patient or the patient's representative. This situation arises only when: (1) the patient is unconscious or otherwise mentally incapacitated; (2) the patient's situation is life threatening and there is no alternative therapy that has an equal or greater likelihood of saving the life of the patient; (3) the experimental intervention must be given almost immediately if it is going to have any chance of success; and, therefore, (4) there is no time to find the patient's representative and obtain informed consent from that representative. The type of research that might fall into this category includes research involving patients who have had a cardiac arrest or traumatic brain injury.

Our overriding principle is that this research, if it is to be done at all, must be done ethically. The requirement that research be done ethically encompasses many factors other than informed consent. For example, research that is not well designed and that cannot lead to definitive scientific answers about the tested drug or device is not ethical. No research should subject any patient to risk without the concomitant benefit of scientific knowledge. Similarly, in all research,

there is a requirement that accurate and full disclosure be given by the investigator to both the Institutional Review Board (IRB) overseeing the research and any patients in the research programs. Full and accurate disclosure requires information about the research purposes, the foreseeable risks, alternative treatments, the possible benefits, and other relevant matters. In addition, once a study is initiated, the investigator has an obligation to adhere to the study protocol that was approved by the IRB. Many of the abuses in research which we have identified were failures to follow the rules requiring truthfulness and faithful adherence to the protocol required of all investigators.

FDA'S STATUTORY RESPONSIBILITIES

FDA regulates clinical research of investigational drugs, biologics, or medical devices under sections 505(i), 507(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act. FDA first imposed informed consent requirements as a result of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, which required that informed consent be obtained in most, but not all, research involving drugs. Later, in 1976, Congress imposed an informed consent requirement for research involving medical devices, which was similar, but not identical, to the informed consent requirement for drugs. In 1981, FDA promulgated informed consent regulations which made the drug and device requirements consistent (Title 21, Code of Federal Regulations (CFR) Part 50).

The essential core of FDA's informed consent regulations is that informed consent must be obtained from a patient or his/her representative in all FDA-regulated research. There is an "exception" to this rule, however, which derives from the device amendments to the law. It permits exceptions from the requirement to obtain informed consent in emergency situations. According to the regulations (21 CFR 50.23(a)), informed consent of the patient or his/her legally authorized representative is required unless the investigator and a physician who is not otherwise participating in the clinical investigation, certify in writing, before the test article's use, that:

1. The patient is confronted by a life-threatening situation necessitating the test article's use.

2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally effective consent from, the patient, for example, if the patient is unconscious. In contrast, a patient's inability to speak a particular language is not considered an inability to communicate.

3. Time is not sufficient to obtain consent from the patient's legal representative.

4. No alternative method of approved or generally recognized therapy provides an equal or greater likelihood of saving the patient's life.

The first three requirements are contained in the device amendments. The fourth requirement regarding the availability of alternative life-saving therapy was added by the FDA to prevent routine reliance on the exception.

The regulatory requirements for exception appear principally directed at individual uses of treatments, and suggest that there must be great confidence in the effectiveness of treatment, i.e., the situation must "necessitate" use of the treatment. They do not apply as easily to clinical trials, especially to a randomized trial where one group gets a placebo instead of the experimental treatment. Nonetheless, the agency has concluded that in some circumstances randomized trials can be conducted in emergency settings under the regulations permitting an "exception" to the requirements for informed consent.

The FDA recently applied these regulations to a clinical trial involving use of an experimental drug for acute head trauma. FDA determined that patients for whom informed consent cannot be obtained, after extensive and well-specified attempts to do so, could be entered in the placebo-controlled trial under an Investigational New Drug Application (IND), consistent with

FDA's informed consent regulations. In these trials, all patients will continue to receive all currently accepted medical intervention for this type of injury; in addition, half the patients will receive the experimental drug, and half a placebo.

This is one area where we plan to give more explicit advice to IRBs and the broader research community, so that they can evaluate carefully and thoughtfully research that is proposed under the regulatory "exception" for informed consent. We also are considering modifications to this part of our regulations, in order to provide more clarity and guidance.

MEDICAL CARE OF PARTICULAR PATIENTS

In my testimony, I have focused principally on the situation where a patient is enrolled in a controlled clinical trial, where some patients receive the experimental drug or device and some do not. We should be mindful that there are situations where a physician may determine that an individual patient might need to be administered an experimental product solely for the purpose of saving the life of that patient, not as part of any research protocol. The FDA has regulations that permit the administration of an experimental product to a patient without informed consent in certain circumstances. If immediate use of the test article is required to save the life of the patient and there is not sufficient time to obtain an independent physician's

determination in advance of using the article, the use must be reviewed and evaluated by a non-participating physician in writing within five working days after the article's use (21 CFR 50.23(b)). This required documentation must be submitted to the IRB within five working days after the test article's use (21 CFR 50.23(c)).

The Department of Health and Human Services' (DHHS) Office for Protection from Research Risks'(OPRR) implements regulations that also address the situation where a physician needs to provide medical care to an individual patient. These DHHS regulations state that, "[n]othing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law" (45 CFR 46.116(f)).

AMBU CARDIOPUMP

One area in which we perceive some confusion on the part of IRBs has to do with their responsibility to ensure that all research on devices that are considered to be "significant risk devices" under FDA's regulations is done under an FDA-approved Investigational Device Exemption (IDE). Under 21 CFR 812.3(m), a significant risk device is defined by FDA as a device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a patient;

2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of the patient;

3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a patient; or

4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a patient.

What we saw with the Ambu CardioPump Resuscitator is that several IRBs, when approached by an investigator who wanted to do research on an unapproved medical device that would be used to attempt to save the life of a patient in cardiac arrest, concurred in the decision that the device was not a significant risk device. That decision was not acceptable under our regulations. A device used to resuscitate a patient in cardiac arrest is surely life sustaining and life supporting and its

failure would present a potential for serious risk to the patient. We advised the company that, by law, they had to cease the research until they had obtained an approved IDE on the Ambu CardioPump.

I would like to stress that the requirement for an IDE was very important here. When we looked at the study design for this device -- indeed the very study design recently described in JAMA -- we found that it was deficient in its randomization, patient evaluations, end points, and other design criteria. This goes back to the basic ethical principle that all research, to be ethical, must be well designed and capable of providing meaningful results.

We are now in the process of examining whether, and when, research on the Ambu CardioPump could be done in the field environment, for example by trained ambulance workers. We think it is clear, however, that before such a study is conducted, preliminary research can be done in a hospital on patients who have given prospective or anticipatory consent. After that we believe field research could ethically be conducted on unconscious patients who are unable to give consent.

FDA is looking at this regulation to determine whether it can be clarified. Alternatively, it may be more useful to provide additional guidance regarding the standards for when an

IDE is required before research can be initiated using an unapproved medical device.

DEFERRED CONSENT

"Deferred consent" is neither defined, nor acceptable, under either FDA or DHHS regulations. This term has been used in the past, however, to describe a procedure whereby patients or representatives of patients are informed, after the fact, that the patient participated, unknowingly, in a clinical investigation of an experimental treatment, and was administered a test article in the course of the clinical investigation. Patients or their representatives are then asked to ratify that participation retroactively, and to agree to continuing participation. Both FDA and OPRR are in agreement that such post-hoc ratification is not true consent because the patient or representative has no means to prevent the administration of the test article, and cannot, therefore, meaningfully be said to have consented to its use.

FDA'S COORDINATION WITH THE OFFICE FOR PROTECTION FROM RESEARCH RISKS

FDA and OPRR have a long history of working together to ensure that patients are protected in research supported, conducted, or regulated by DHHS. For more than a decade, the two agencies have cosponsored numerous workshops to educate members of IRBs on our respective regulatory requirements, co-produced a series of videotapes on protecting patients in research, developed written information explaining the regulations to the IRB community, and worked to harmonize our regulations. This latter effort has been done in recognition that many researchers and IRBs must comply with both FDA and DHHS regulations in the conduct of research.

Generally, FDA and DHHS informed consent regulations are very similar. There are, however, a few differences between these regulations on the issue of informed consent.

The DHHS informed consent regulations (45 CFR 46.116(d)) provide different criteria than FDA's regulations under which an IRB may make an exception to the requirements for obtaining informed consent. The OPRR regulations contain a provision that permits the IRB to "waive" the requirement to obtain informed consent provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the patients;

2. The waiver will not adversely affect the rights and welfare of the patients;

3. The research could not practicably be carried out without the waiver; and

4. Wherever appropriate, the patients will be provided with additional pertinent information after participation.

"Minimal risk" in both FDA and DHHS regulations means that, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." This definition is a key factor in the DHHS regulations. Whether to permit the waiver of informed consent in a particular research activity, and deciding whether the risks of treatment should be considered minimal, is a critical responsibility of IRBs. In FDA's regulation, the definition of minimal risk relates mainly to whether the IRBs can expedite the review of the research protocol. See 21 CFR 56.110. Minimal risk is not used as a factor in determining whether informed consent can be waived.

We recognize that some IRBs need more direction relating to how they can properly evaluate research under both the FDA and DHHS regulations. We have already raised these issues with OPRR, and intend to work with them on whatever educational and other efforts are necessary, to eliminate any confusion.

HOW COULD RESEARCH BE DONE ETHICALLY WITHOUT PRIOR INFORMED CONSENT

There is currently a great deal of debate in the ethics or research community as to how research could be ethically conducted in the acute care context. Clearly, any research that can build in a requirement for informed consent must do so. Frequently, there are ways to design a study so that one is not confronted with emergency situations in which consent cannot be obtained. In some instances, an individual may be comatose, but immediate treatment is not needed in order to prevent death or irreparable harm. In those instances, it may be possible to delay treatment until a court appointed patient-advocate is arranged, next-of-kin are located, or some other procedure can be followed. Anticipatory consent may be obtained upon non-emergency admission to a hospital. If a study can be designed so that informed consent can be obtained, that should be done.

In other cases, however, an investigator cannot obtain prior informed consent. FDA recognizes, however, the need to study

promising therapies used specifically by populations that present difficulties obtaining informed consent because of the nature of their illness. We are exploring the complex ethical questions involved in such studies. We are very conscious of the need for rigorously designed studies to obtain data on interventions in acutely life-threatening situations such as cardiac arrest and traumatic brain injury and do not wish to impede them. Without such studies, new therapies for critically injured patients may never be validated or used. Alternatively, such therapies could become widely used without any rigorous demonstration of their effectiveness through clinical trials.

At the same time, we recognize the legal and ethical need to ensure that patients are protected. The current FDA and OPRR informed consent regulations are based, in large part, on the ethical principles discussed in the Belmont Report, prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978. As discussed in that report, the three basic principles that are particularly relevant to the ethics of research involving human subjects are the principles of respect for persons, beneficence, and justice.

Respect for persons incorporates at least two basic ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. Persons are treated in an

ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. Such treatment falls under the principle of **beneficence**. In the Belmont Report, beneficence is understood as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do no harm; and (2) maximize possible benefits and minimize possible harms.

The principle of justice relates to who ought to receive the benefits of research and its burdens. There are several formulations of just ways to distribute burdens and benefits: (1) to each person an equal share; (2) to each person according to individual need; (3) to each person according to individual effort; (4) to each person according to societal contribution; and (5) to each person according to merit. The Report also notes that:

> These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

In March 1983, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral

Research issued its "Second Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subjects." In its identification of "Issues Worthy of Further Consideration," the President's Commission identified research on the comatose as one of its topics. It notes that:

> It is settled law that physicians and hospitals may assume that an emergency patient would consent to life-saving treatment; such treatment may therefore be initiated without express consent. The legal principle is based, however, on the provision of standard care. It is not so clear, however, whether one should assume that an emergency patient would consent to participation in research on new or experimental treatment.

We think that it is time for us to reexamine our regulations in light of advances in technology that have brought new treatments for previously untreatable conditions but for which patients cannot give consent. Moreover, in 1978, it appears the major if not sole concern was protecting vulnerable patients so that they would not be used as "guinea pigs." Investigational products were viewed from the standpoint of their risks and an attitude some would consider paternalistic prevailed. In the 1990's, this emphasis has begun to be supplemented by an emphasis on the right of an individual to have access promising new

therapies. Clearly, both protection, especially of a patient with no ability to protect himself or herself, and access to potentially life-saving treatment are important. A public policy consensus on exactly how to balance these has not yet emerged.

We believe that it is important to define and seek some consensus on precisely how, and in what circumstances, patients who cannot give consent can be enrolled ethically in such research. In light of this, FDA is reviewing its informed consent regulations and is exploring with the National Institutes of Health (NIH) ways to obtain broad public input in an attempt to reach some consensus on the circumstances under which specific research activities may be justified when prior informed consent cannot be obtained. As we review our regulations and practices, we also will coordinate with any other Federal bodies that will be considering similar informed consent issues.

We intend to sponsor a workshop jointly with NIH so that we will have a forum for interested patients, physicians, ethicists, and members of IRBs to express to us their concerns and suggestions. As part of this workshop, we hope to convene a group of experts who will be able to discuss the very complicated ethical issues raised by this type of research.

As part of this process we will examine the types of safeguards that could be put in place to protect the rights of

the comatose patient. For example, we will explore alternative protection schemes such as the use of a consent monitor or consent monitoring board that could review the "consent" records for the study, or publicizing the details about the study ahead of time so that society could debate its merits. We also will look at additional safeguards that need to be in place, regarding both the type and design of the research, as well as the qualifications of the physicians who could participate in the research.

FDA'S BIORESEARCH MONITORING PROGRAM

The FD&C Act requires that certain products, such as new human drugs, medical devices, food additives, and veterinary drugs, be approved by FDA before they can be marketed in interstate commerce. In order to obtain approval from FDA, extensive data concerning the safety and/or efficacy of the product must be submitted to FDA. These data are obtained through research conducted at multiple sites, and is often referred to as FDA-regulated research because of the regulatory requirements FDA has regarding its conduct and reporting.

FDA monitors and inspects all aspects of the conduct and reporting of FDA-regulated research through a comprehensive program of on-site inspections and data audits. The objectives of the bioresearch monitoring (BIMO) program are to protect the

rights and welfare of human research subjects and to verify the quality and integrity of data submitted to FDA in support of marketing applications. Last year, we conducted approximately 1000 inspections under the program.

The BIMO program is implemented through the following compliance programs: (1) Good Laboratory Practice (GLP) Program (Nonclinical Laboratory); (2) Clinical Investigator Program; (3) Institutional Review Board (IRB) Program; (4) Sponsor, Contract Research Organization and Monitor Program; and (5) In Vivo Bioequivalence Program.

Institutional Review Board (IRB) Program

FDA's IRB Program is unique among our BIMO programs in that its primary focus is on ensuring protection of the rights and welfare of research subjects, rather than validating the data obtained from research. FDA requires that all FDA-regulated research involving human subjects be reviewed, approved, and monitored by an IRB in accordance with 21 CFR part 56. An IRB is any group formally designated by an institution to approve the initiation of, and periodically review, biomedical research involving human subjects to be conducted at the institution. The primary purpose of the IRB review is to ensure protection of the rights and welfare of the patients. The IRB is responsible

for approving the informed consent form and procedures for ensuring that the clinical investigators obtain informed consent in a manner that complies with FDA's informed consent regulations.

FDA's regulations contain the general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations submitted to FDA under sections 505(i), 507(d), and 520(g) of the FD&C Act. IRBs, however, are not required to register with FDA nor inform FDA when they begin reviewing studies. Sponsors are required to inform the agency about the IRBs they use for these studies.

FDA's IRB Program provides for periodic inspections of IRBs for compliance with FDA's protection of human subjects and IRB regulations (21 CFR part 50 and 56, respectively), i.e., requirements for IRB membership, record keeping, procedures, informed consent, etc. The frequency of the inspections depends on the performance of the IRB and the number of critical studies it is monitoring. These inspections are announced in advance. Due to the often voluntary nature of IRB membership and the public service IRB members perform, FDA's approach to these inspections traditionally has emphasized obtaining compliance through

education and cooperation rather than through strict application of regulatory or administrative sanctions.

Administrative sanctions are imposed, however, in significant cases of noncompliance. Significant noncompliance generally means cases where the institution or the IRB failed to adequately protect the rights and welfare of the subjects, such as by inadequately obtaining informed consent. These sanctions include restricting the IRB from approving any additional studies or allowing admission of more patients to ongoing studies until corrections are made. In the most extreme cases of noncompliance, an IRB may be disqualified from serving as an IRB (i.e., reviewing or approving any clinical research submitted to the agency). To date, no IRBs have been formally disqualified by FDA, although over 30 voluntarily have ceased operations following FDA inspections. It has been demonstrated, however, that IRBs being reinspected are more often found to be in compliance than those being inspected for the first time.

Deficiencies in the informed consent document are found in approximately three-fourths of FDA's IRB inspections. The most common deficiencies in the informed consent document are: (1) lack of clarity about the person to contact if there are questions concerning the research and

the research subject's rights in the event of a research-related injury; (2) inadequate description of the research procedures to be followed; (3) inadequate description of compensation if the subject sustains injury as a result of the research; (4) inadequate confidentiality statement; and (5) inadequate description of alternative procedures that are available to subjects should they choose not to participate in the research.

Recent IRB Administrative Actions for Noncompliance

The following are recent examples of administrative actions FDA has taken with respect to IRBs for noncompliance with the agency's IRB regulations (21 CFR part 56).

University of California, San Diego - On February 14, 1994, FDA sent a warning letter to the University of California, San Diego, citing failure of the University and its IRB to protect adequately the rights and welfare of patients in research. This letter suspended the authority of the IRB to approve new studies, (under 21 CFR 56.120(b)(1)), and directed that no new patients be added to ongoing studies, (under 21 CFR 56.120(b)(2)).

The University was instructed to: (1) ensure that the IRB receives and acts on all reports of unexpected adverse

events in order to protect adequately the rights and welfare of all patients involved in the research; (2) ensure that the IRB and the principal investigators are informed of their mutual responsibilities for initial and continuing review of IND studies, especially the timely submission and review of all progress reports; and (3) ensure that the informed consent documents (ICDs) meet FDA requirements and that the clinical investigator only uses ICDs approved by the IRB.

On March 4, 1994, FDA lifted its restrictions against the University after it agreed to correct the problems the agency had found and documented the plan to accomplish this objective. At that time, FDA gave the University approval to again approve studies and add new patients to ongoing studies. FDA will reinspect the University and its IRB within one year to determine whether they are complying with our IRB regulations.

IRB for Florida Clinical Research - On March 25, 1994, FDA sent a warning letter to Florida Clinical Research, in Coral Springs, Florida. This letter suspended the authority of its IRB to approve new studies, (under 21 CFR 56.120(b)(1)), and instructed the IRB not to add any new patients to ongoing studies, (under 21 CFR 120(b)(2)). FDA also requested the IRB to notify immediately the principal

investigators not to add any new patients to their ongoing studies.

The IRB's most significant violation was that it met and approved IND studies at meetings where none of its four physicians were invited to attend, nor present. The presence of a physician is essential to evaluating the risk/benefit ratio of proposed IND uses.

On April 12, 1994, Florida Clinical Research submitted revised written operating procedures for the IRB. FDA reviewed and accepted these revised procedures and on April 15, 1994, the agency lifted its restrictions on the IRB.

Clinical Investigator Program

The Clinical Investigator Program conducts study-specific inspections and audits of physicians, veterinarians and other investigators conducting clinical trials of FDA-regulated products. The primary regulatory obligations of the clinical investigator are to: (1) follow the approved protocol or research plan; (2) obtain informed consent and adhere to FDA regulations regarding protection of patients; (3) maintain adequate and accurate records of study observations; and (4) administer test articles only to

patients under control of the investigator. The investigator also is responsible for ensuring that the study is reviewed and approved by an IRB initially and on a continuing basis.

The agency inspects at least two of the most important investigators in a study. These inspections and audits are announced in advance and consist primarily of examining study records and findings, with particular attention given to protocol adherence. They include a review of the patient files for documentation of informed consent and review of the correspondence files for documentation of IRB review, approval and continued monitoring.

In 1993, FDA performed approximately 550 clinical investigator inspections. Regulatory or administrative follow-up actions include rejection of the study, disqualification of the investigator (five in 1993), and/or criminal prosecution in cases of deliberate fraud.

Sponsor, Contract Research Organization and Monitor Program (Sponsor/Monitor Program)

The Sponsor/Monitor Program is a general surveillance program that provides for inspections of those parties responsible for initiating, overseeing, and reporting the

results of clinical research to FDA. A sponsor is usually an organization, corporation, or individual who is responsible for initiating clinical investigations but does not usually conduct the investigation. They are responsible for submitting the research application and designing, directing, monitoring, evaluating and reporting the results of all research conducted in support of the application. The sponsor is permitted to transfer responsibility to contract research organizations (CROs) or monitors. Such organizations are under the same regulatory obligations as the sponsor. Monitors are those individuals who the sponsor or CRO selects to oversee the clinical investigation and may be an employee of the sponsor or CRO.

Inspections under this program are conducted without pre-notification, unlike our IRB and clinical investigator inspections. These unannounced inspections include audit of records and interviews with the sponsor, CRO, or monitor in order to evaluate regulatory compliance and to validate data.

In 1993, FDA conducted 60 sponsor/monitor inspections. Noncompliance may result in termination of existing exemptions to conduct research, rejection of studies, seizure of test articles remaining in commerce after

termination of exemptions, injunction, and criminal prosecution.

FDA EDUCATIONAL EFFORTS

FDA has tried to be responsive not only to the needs of the IRBs, but also to the needs of patients, clinical investigators, institutional administrators, industry, and others. In this effort, FDA widely distributes written guidance and participates in regional workshops to help educate these groups in order to ensure that research is conducted in an ethical manner that protects the rights and welfare of patients.

CONCLUSION

FDA recognizes the importance of its ethical and legal obligations to protect the rights of patients. At the same time, there is a significant need to evaluate promising therapies used by patients from whom informed consent cannot be obtained. Consequently, we are reviewing our informed consent regulations and are exploring with NIH ways to obtain the broad public input that is necessary to reach a consensus on the criteria that should be used to permit research on these patients. We would be happy to answer any questions you have about FDA's oversight of medical research involving informed consent.

TESTIMONY OF MICHELLE BIROS, M.D.
HENNIPEN COUNTY MEDICAL CENTER
MINNEAPOLIS, MINN.

Testimony of the Society for Academic Emergency Medicine
May 23, 1994

INTRODUCTION:

This written testimony is provided for the public record by the Society for Academic Emergency Medicine (SAEM). Our membership includes more than 2800 academic Emergency Physicians, and our mission is the improvement of the emergency, urgent, and critical care of the acutely ill or injured patient through the promotion of responsible research. The Society for Academic Emergency Medicine is committed to the conduct of well designed , well monitored clinical research studies , and we are unwavering in our support of patient rights and protection during research. While we realize that isolated cases of abuse may occur during the performance of human subjects research, we want to take this opportunity to look beyond these rare instances in order to address additional concerns which we have as clinicians who do research on the diseases of the acutely ill and injured. This statement will express our general ethical beliefs, point out problems which we have encountered in conducting research within current regulatory guidelines, and suggest why some abuses could and may have occurred. We also will propose suggestions which we believe may reduce confusion for acute care researchers and their Institutional Review Boards, especially when such research involves incapacitated patients unable to provide prospective informed consent to participate in acute resuscitation research. We appreciate the opportunity to present our thoughts on these issues of great importance to our patients. We applaud this subcommittee's identification of the inconsistencies , lack of definition, and need for reexamination of the current regulations to accommodate responsible, ethical and necessary acute care research.

SCOPE/RELEVANCE

Americans deserve and expect modern, safe, and effective medical care when they are acutely ill or injured. Moreover, the public expects medical advances. We believe the American public understands that improving medical care requires biomedical research. As emergency physicians, our obligation to society includes both providing care to critically ill or injured patients, and insuring that the quality of this care is improving. Therefore we believe that the public mandate for improvements in acute care medicine necessitate research into the causes and treatments of these illnesses.

Before the modern medical era, patients who were critically ill, to the point of being unable to communicate with their physicians, usually died. Because of the progress in medical therapies, largely from the results of clinical research trials, we now are able to effectively

treat many such patients . For example, thousands of patients are resuscitated each year in the prehospital setting with electrical defibrillation, now a standard of medical care for the treatment of cardiac arrest due to ventricular fibrillation. All of the studies which led to the development of this life saving therapy and its acceptance as a standard of care were done in unconscious patients , unable to give prospective informed consent to participate in the research. Even so, survival rates for this condition are no better than 8 -18 %. Clearly, for this and other conditions, more progress must be made to augment present therapies that are largely ineffective.

Because of our previous research, our knowledge of the pathology of many life threatening illnesses and injuries is expanding, and we are now in a position to test new therapies for many devastating critical medical conditions. These conditions include, but are not limited to, severe head trauma, cardiac arrest, severe penetrating trauma, and stroke. Most therapies which have potential benefit for these conditions will be useful only if they are delivered within a short time after the onset of the problem. A patient starts to suffer irreversible neurologic damage within minutes of suffering a cardiac arrest; after closed head injury brain swelling may occur within tens of minutes; and brain cells deprived of blood flow because of a stroke are probably irreversibly damaged within an hour. The decision to provide these patients with a potential new therapy cannot, in these circumstances, be delayed by very long. In addition, the ability of the patient to consent to the research is compromised because of the acute medical condition. Whether we are conducting clinical research of new and promising therapies, or simply trying the only current therapy available, the therapy must be instituted prior to informed consent by a legal surrogate. Under these circumstances, decisions must be made immediately on behalf of the patient .

In all situations when decisions affecting a vulnerable population are made by people outside that population, there is potential for misuse and abuse. Treatment with a test article may put incapacitated patients at some added risk in the absence of appropriate safeguards for patients who are unable to speak for themselves .The consequence of not doing acute resuscitation research is also a risk to society as a whole, as well as the incapacitated patient who is critically ill or injured who may benefit from a new treatment . Thus it is imperative that regulatory agencies, ethicists, and leaders in Emergency Medicine and Critical Care research work together to define both the standards which all emergency research must meet, and the regulatory mechanisms to insure that such standards are enforced. Just as Emergency Medicine physicians set the standards for the ethical and

equal treatment of patients without respect to their ability to pay, we must set the ethical standard for the conduct of research involving patients who have suffered a loss of autonomy by becoming incapacitated by illness or injury.

ETHICS

Three fundamental ethical principles guide the conduct and regulation of research: respect for persons, beneficence, and justice.

1. Respect for persons affirms that individuals have the right to determine what will be done to them; this principle expresses the concept of autonomy. Respect for persons also recognizes that certain groups of persons have decreased capacity to make this determination and therefore are in need of special protection.

2. Beneficence arises from the primary obligation to do no harm and is expressed further as the dual obligation to maximize possible benefits and minimize possible harms. Both individual and societal benefits may be considered; the obligation to not cause individuals harm outweighs societal benefits.

3. Justice requires that persons are treated fairly; sharing both burdens and benefits demands that risk of harms not be assumed by persons who are unlikely to benefit from the research.

By the time a new treatment has advanced to the point of human clinical studies, it has already undergone trials of safety under controlled laboratory and clinical settings. Safety trials should always be conducted on non-vulnerable populations prior to the start of efficacy studies. The effectiveness of new treatments are compared to other standard treatments or placebo only when a reasonable safety profile has been established. Often, acutely ill or injured patients who might benefit from the experimental treatment are unable to give consent and the opportune window of time in which the treatment is useful useful is too brief to allow identification of a surrogate to provide prospective proxy. Other questions of research ethics then emerge. Should only those critically ill or injured patients for which a surrogate can be found be allowed to receive potentially beneficial therapy for life threatening events? This approach may conflict with the concept if justice, as delineated in the Belmont report. Should only those therapies which can be delayed in administration be studied for life threatening situations, thus reducing the potential benefit of stopping or

reversing a pathological process early in its escalating devastating course? The concept of beneficence makes this approach unsatisfactory.

Regardless of whether prospective informed consent is obtained, or consent is waived, a clinical trial is only ethical if it is truly unclear to a medical expert which of the two treatments being compared is most likely to be more effective or which treatment would be preferred by an informed, competent, and reasonable patient. Any studies in which one therapy being tested was known to be inferior to the other would be unethical, regardless of whether informed consent was obtained prospectively.

Health and Human Services regulations governing research are based in these fundamental ethical principles: the purpose of these regulations is to protect the rights and welfare of human participants in research. Confusion and inconsistencies surrounding these regulations, and lack of IRB guidelines for their interpretation have contributed to some cases of perceived research abuse.

THE CURRENT PROBLEM DEFINED

The primary barrier to the effective and uniform enforcement of regulations aimed at protecting human subjects from unethical research involving lack of informed consent is the regulatory language contained in 45 Code of Federal Regulations (CFR) Part 46.116 and 21 CFR 50.23. While the regulations from Health and Human Services (45 CFR 46.116) were intended to allow waiver of consent under specific circumstance including clinical research, the Food and Drug Administration (FDA) regulations in 21 CFR 50.23 were intended only to allow a waiver of consent for a one time therapeutic use of an investigational agent in a life-threatening situation. The differences in intent have lead to differences in interpretation by IRBs, which lack guidance from the regulators.

The regulations in 45 CFR 46.116 include, as a requirement for a possible waiver of informed consent, that the research pose no more than "minimal risk" to the subject. While the term "minimal risk" has been defined conservatively as the risk encountered by people in their usual daily activities, that risk standard has no bearing on a critically ill or injured patients, such as one who has suffered serious closed head injury or whose heart has stopped beating. A better definition of minimal risk would be risk that is minimal when compared to the natural course of their current medical condition, so that there is minimal added risk to the patient in his current condition. We believe that IRBs should be guided to use the concept of " incremental " or " added " risk in their assessment of research

which holds promise in the face of an emergent devastating condition for which no current therapy is satisfactory.

A clinical study must be well designed to allow an impartial but accurate assessment of the effectiveness of the new therapy compared to the current standard therapy. Just as we have an ethical imperative to provide the best possible medical care to critically ill and vulnerable patients, we have an ethical obligation to insure that at the end of a clinical trial we can draw a reliable, unbiased conclusion concerning which therapy should be applied to future patients. The FDA regulations in 21 CFR 50.23 require , for use of a waiver for consent, that a life-threatening event exists that necessitates use of the test article. While most of the Emergency Medicine research that is affected by these regulations does involve the treatment of life-threatening events, it is difficult to argue that such events ever necessitate the use of a test article that includes a placebo. Many consider a placebo to be no treatment. In fact, those patients who are randomized to receive a placebo during a controlled clinical trial receive the same care as patients not in a study who have the same medical conditions. It is critically important that placebo-controlled trials be conducted when testing therapies for devastating conditions. When placebo controls are not used, the results of clinical trials are often misleading. Unless randomization is employed in clinical trials, the potential for bias for or against a test article is always present. Federal regulations should consider the possibility that therapies must be compared to each other in a randomized manner in life-threatening situations. Of course, it would never be ethical to withhold known effective treatment for the patient's condition.

There is a need for continued vigilant oversight of clinical trials of acute resuscitation research. Local IRBs, with good insight into local practice, patient population, and capabilities of local researchers , institutions and resources, are the monitoring bodies that are responsible for this oversight. Clarification and definition of current federal regulations would allow easier and more consistent IRB interpretation of those regulations involving human subjects research, and reduce the likelihood of research abuse in clinical trials.

STEPS TOWARDS RESOLUTION

As clinicians who do acute resuscitation research, we offer the following proposals to address some of the concerns mentioned above;

1) The federal regulations need to be re-examined in the content of the current medical climate. The current regulations were written before the rapid advancement of the fields

of emergency and critical care. Ethical options for research involving patients who are unable to give consent, must be considered for prehospital, emergency, and critical care research. Federal regulations should address these options, both to satisfy the public's mandate for effective treatment of illness and injury, and to allow sufficient protection to potential research subjects who have lost their ability to act autonomously and are thus vulnerable.

2) There needs to be a consensus between the FDA and the OPRR regarding interpretation of current regulations. Both agencies are under the auspices of HHS, yet each has different intents in those regulations governing the waiver of informed consent. We call for a consensus conference between the agencies, representatives of IRBs, and researchers interested in acute resuscitation research.

3) Current regulatory terms need to be defined in ways germane to acute care research in order to provide IRBs with the information needed to make reasonable and consistent judgments concerning the risk - benefit ratio of the proposed research.

4) Institutional review boards need additional guidance from the regulatory agencies to allow appropriate interpretation and application of the federal regulations.

SUMMARY

We have an obligation to improve the medical therapies that we offer critically ill and injured patients. It is only through controlled comparative trials that such improvement may occur. Because of the rapidity with which the most promising therapies must be administered, such research will necessarily involve waiver of prospective informed consent. Society must weigh the risks and benefits of acute care research and provide guidance to researchers and regulators on acceptable safeguards to protect the autonomy of incapacitated patients , while still providing them the opportunity to receive promising therapy when no effective treatment is known.

The present federal regulations in 45 CFR 46.115 and 21 CFR 50.23 do not directly and consistently guide institutional review boards (IRBs) in the review and regulation of acute care studies. In order to obtain clear guidance for the review and regulation of such studies, the federal regulations will need revision specifically aimed at modifying the concept of minimal risk and authorizing the randomization of drug therapies in critically ill patients.

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